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CONTENTS

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ORIGINAL REPORTS

continued on following page

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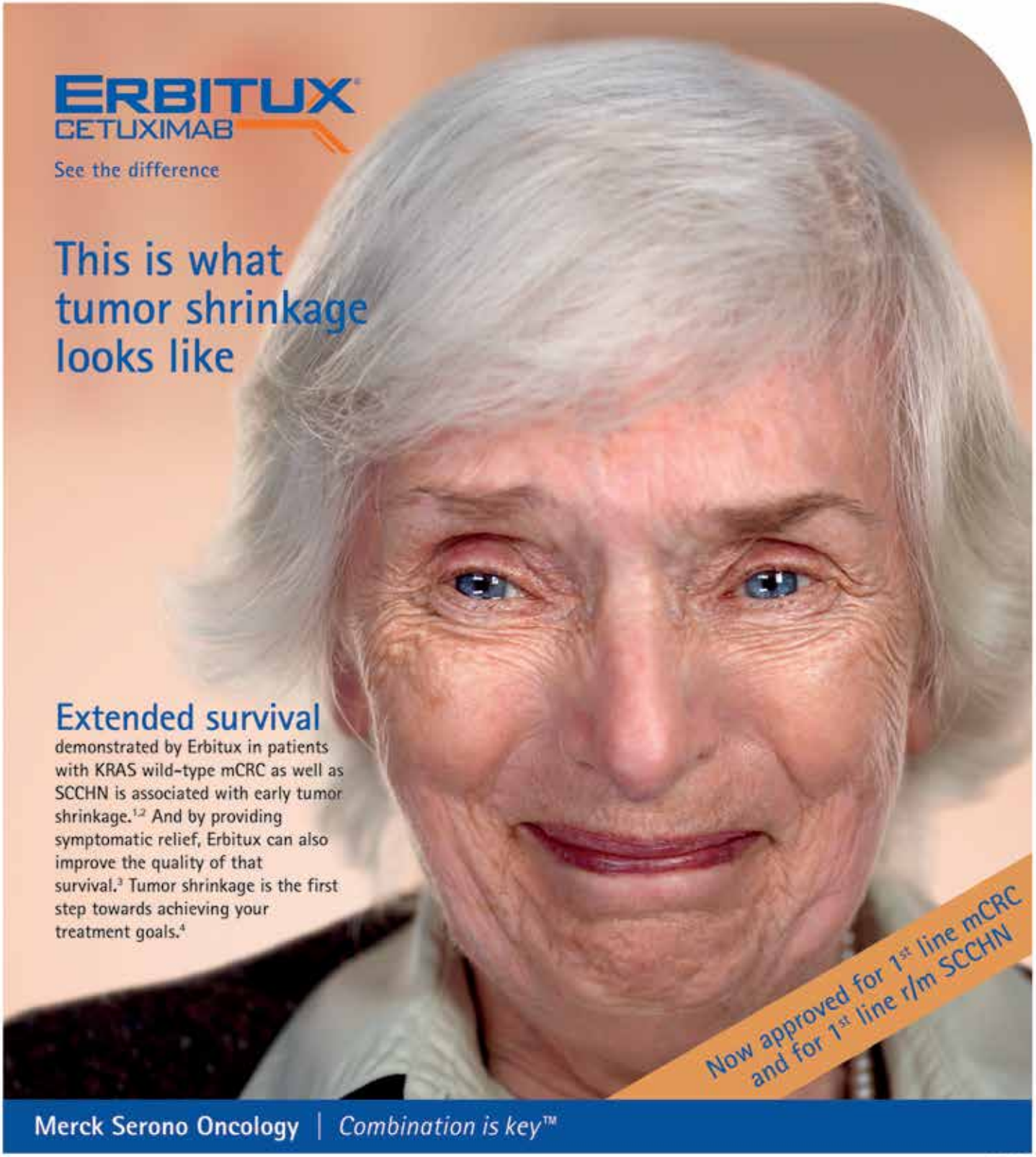

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COMMENTS AND CONTROVERSIES

Locoregional Radiotherapy in Patients With Breast Cancer Responding to Neoadjuvant Chemotherapy: A Paradigm for Treatment Individualization

Julia White, *The Ohio State University Comprehensive Cancer Center, Columbus, OH*
Eleftherios Mamounas, *MD Anderson Cancer Center Orlando, Orlando, FL*

See accompanying article on page 491

The increasing use of neoadjuvant chemotherapy for patients with breast cancer with axillary nodal metastases has created debate among multidisciplinary tumor boards centered on the optimal use of locoregional radiotherapy. Clinical decision making regarding the use of postmastectomy and regional nodal radiotherapy has been built on evidence from numerous randomized clinical trials where pathologic staging from upfront surgery was the determinant of receiving treatment after adjuvant chemotherapy.[1] It is generally recommended that patients who have axillary nodal metastases receive radiotherapy to the chest wall and regional nodes after mastectomy or to breast and regional nodes after lumpectomy. Conversely, in patients with negative axillary nodes, radiotherapy is not typically recommended after mastectomy and is confined to the breast alone after lumpectomy. The absence of similar evidence in the setting of neoadjuvant chemotherapy has led to conflicting opinions about the key factors that should drive the clinical decision to administer locoregional radiotherapy. The thoughtful concepts of Marks and Prosnitz[2] endorse the concept that the prechemotherapy-positive axillary nodal metastases are the key factor and caution that reducing radiotherapy based on chemotherapy response places women at risk for worse breast cancer mortality. Conversely, others have supported the idea that pathologic nodal status postchemotherapy is the important factor and argued that for patients who become pathologically node negative after neoadjuvant chemotherapy, radiotherapy may not offer significant benefit.[3] It is clear that the absence of evidence permits the generation of disparate treatment recommendations for the same clinical scenario, placing women at risk for either over- or undertreatment.

As stated by Marks and Prosnitz,[2] the critical threat of suboptimal locoregional cancer treatment is that it will result in worse breast cancer survival. Significant evidence exists that the addition of locoregional radiotherapy after upfront surgery and adjuvant chemotherapy can improve breast cancer survival in addition to providing large gains in locoregional cancer control.[1,4,5] The Early Breast Cancer Trialists Collaborative Group (EBCTCG) 2005 meta-analysis studied the effect of radiotherapy on locoregional recurrence at 5 years and breast cancer mortality at 15 years. This demonstrated that the absolute benefit in reducing breast cancer mortality resulting from radiotherapy was related to the magnitude of locoregional risk in the nonirradiated patients. However, an analysis that divided absolute locoregional recurrence risk reduction after lumpectomy or mastectomy by 5 years into three categories of $< 10\%$, 10% to 20%, or $> 20\%$ demonstrated that for those with $< 10\%$ absolute reduction in local recurrence resulting from radiotherapy by 5 years, there was no improvement in breast cancer mortality by 15 years.[1] Similarly, the EBCTCG 2011 meta-analysis demonstrated that the reductions gained in 10-year overall breast cancer recurrence rate (local, regional, and distant) by postlumpectomy breast radiotherapy resulted in improvement in 15-year breast cancer mortality rate.[6] An analysis that stratified the predicted absolute reduction in 10-year overall breast cancer recurrence risk from radiotherapy into groups of low ($< 10\%$), intermediate (10% to 19%), and large ($> 20\%$) found in the low-risk group an absolute reduction of 6.9% with radiotherapy (18.9% without *v* 12% with radiotherapy), corresponding to a negligible absolute reduction in 15-year risk of death resulting from breast cancer of 0.1% (-7.5% to 7.7%). Collectively these analyses support that the survival benefit from radiotherapy after upfront surgery and chemotherapy is related to an individual patient's risk of any recurrence based on clinical and pathologic features. It is recognized that the extent of response to neoadjuvant chemotherapy is associated with prognosis, with the best relative disease-free survival occurring in those who achieve a complete pathologic response.[7] Therefore, it is logical that if upfront chemotherapy can place a patient in a sufficiently low risk category for locoregional recurrence after surgery, then adding radiotherapy will not significantly reduce the risk of breast cancer mortality.

There is supporting evidence that neoadjuvant chemotherapy response is linked to lower rates of subsequent locoregional recurrence risk in the absence of radiotherapy. Mamounas et al[8] analyzed locoregional recurrence rates in approximately 3,000 women enrolled onto two National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials evaluating neoadjuvant chemotherapy (NSABP B-18 and NSABP B-27). Both protocols specified that patients treated with lumpectomy were required to receive breast radiotherapy only, and patients treated with mastectomy were not allowed to receive any radiotherapy. The combined analysis of these two trials provides important information on the rates, patterns, and independent predictors of locoregional recurrence after neoadjuvant chemotherapy. The 10-year cumulative incidence of locoregional recurrence was 12.3% for patients who underwent mastectomy (local, 8.9%; regional, 3.4%)

and 10.3% for patients who underwent lumpectomy and received breast radiotherapy (local, 8.1%; regional, 2.2%). Independent predictors of locoregional recurrence in patients undergoing lumpectomy were age, clinical nodal status, and pathologic nodal status/pathologic breast response; for those undergoing mastectomy, they were clinical tumor size, clinical nodal status, and pathologic nodal status/pathologic breast response. In particular, women who had clinically involved nodes before chemotherapy who were pathologically node negative at surgery (with or without pathologic complete response in the breast) had lower locoregional recurrence than those who were found to have persistent nodal metastases pathologically. More specifically, in 224 patients who underwent breast-conservation therapy with clinically positive nodes before neoadjuvant chemotherapy and pathologically negative nodes afterward, the risk of regional nodal recurrence was low, between 0% and 2.4%, and the risk of local recurrence in the breast was 7% to 10% at 10 years. Similarly, in 102 patients undergoing mastectomy with clinically positive nodes before neoadjuvant chemotherapy and pathologically negative nodes afterward, the risk of chest wall and regional nodal recurrence was between 0% and 10.8%. These locoregional recurrence rates fit into a low-risk category of patients who are unlikely to experience improved overall survival from radiotherapy. It is important to emphasize that the results of the combined analysis of NSABP B-18 and B-27 are primarily applicable to patients with clinical stage I to II disease; 55% of the patients presented with cT1-2N0 disease, 20% with cT1-2N1 disease, and 16% with cT3N0 disease. Only 9% of the patients presented with cT3N1 disease.

Higher rates of locoregional recurrence have been demonstrated in patients who present with clinical stage $\geq$ III disease, even if they achieve a pathologic complete response after neoadjuvant chemotherapy. McGuire et al[9] reported locoregional recurrences in a group of 106 women achieving a pathologic complete response from neoadjuvant chemotherapy, 74 of whom initially had clinical stage IIIA, B, or C disease. For those who initially presented with stage III disease, locoregional recurrence at 10 years was 33.3% without radiotherapy versus 7.3% with radiotherapy ($P = .040$); howevefr, similar locoregional recurrence rates were seen with or without radiotherapy in the group that presented with clinical stage I or II disease before chemotherapy.

The results of the combined analysis of NSABP B-18 and B-27 clearly demonstrate that in addition to age and clinical stage before neoadjuvant chemotherapy,[8] pathologic response in the breast and axillary nodes has a major impact on the rate of locoregional recurrence and in fact seemingly minimizes the effects of age, clinical tumor size, and nodal status before neoadjuvant chemotherapy. Specifically, in patients who have positive nodes before neoadjuvant chemotherapy, the rate of locoregional recurrence can be modified downward if the nodes become pathologically node negative after neoadjuvant chemotherapy (particularly if there is also pathologic complete response in the breast). The NSABP B51/RTOG (Radiation Therapy Oncology Group) 1304 phase III clinical trial (NCT01872975) is designed to answer whether regional radiotherapy improves the invasive breast cancer recurrence–free interval rate (local, regional, and distant recurrences and deaths resulting from breast cancer) in women who present with clinical N1 axillary nodal disease (documented pathologically by needle biopsy) before neoadjuvant chemotherapy and then become pathologically node negative at time of surgery. After mastectomy, patients are randomly assigned to no radiotherapy versus chest wall and regional nodal radiotherapy, and after lumpectomy, random assignment is to breast radiotherapy alone versus breast and regional lymph node radiotherapy. Patients with high-risk breast cancer at presentation, clinical stage N2 to 3 disease, or stage IIIB or C disease are not eligible. The results of this clinical trial have the potential to produce a major paradigm shift in the locoregional management of early-stage breast cancer, namely by providing evidence for presence or absence of benefit from regional radiotherapy when pathologic downstaging of the axillary nodes by neoadjuvant chemotherapy occurs.

For women who receive neoadjuvant chemotherapy and whose lymph nodes remain pathologically positive after surgery, regional radiotherapy is indicated. However, these women can be enrolled onto the ALLIANCE (Alliance for Clinical Trials in Oncology) A011202 phase III clinical trial (NCT01901094) that is designed to answer whether axillary node dissection improves the rate of breast cancer recurrence over that seen with sentinel node biopsy alone when regional radiotherapy is delivered. Together, these trials will potentially allow us to fulfill our commitment to patients with breast cancer who receive neoadjuvant chemotherapy—to achieve maximal breast cancer survival while tailoring locoregional treatment to best fit their disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Final approval of manuscript: All authors

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COMMENTS AND CONTROVERSIES

Reducing Local Therapy in Patients Responding to Preoperative Systemic Therapy: Are We Outsmarting Ourselves?

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See accompanying article on page 494

There is growing interest in the use of preoperative (neoadjuvant) chemotherapy for patients with localized breast cancer.[1,2] Originally, it was hypothesized that such early use of chemotherapy might improve survival, compared with standard postsurgical adjuvant systemic therapy, but this has not proven to be the case.[2] Nonetheless, the primary tumor response is likely a barometer for tumor sensitivity to therapy and may be used to help guide decisions regarding additional systemic therapy. Furthermore, preoperative chemotherapy can increase the fraction of women eligible for breast-conservation therapy.[3]

A seemingly logical extension of this latter observation is the hypothesis that one can further reduce local therapies in patients responding well to initial chemotherapy.[4,5] For example, studies are under way to omit (or limit) radiotherapy (RT) in patients who present with positive axillary nodes and experience pathologic complete response in the nodes to preoperative chemotherapy (eg, NSABP [National Surgical Adjuvant Breast and Bowel Project] B-51/RTOG [Radiation Therapy Oncology Group] 1304). In the NSABP/RTOG study, patients with involved axillary nodes (histologically confirmed) are treated with neoadjuvant chemotherapy. Those who are node negative at subsequent mastectomy are randomly assigned to ± postmastectomy RT (PMRT) to the chest wall and regional nodes. Similarly, patients who undergo subsequent breast conservation surgery and whose nodes have become negative after preoperative chemotherapy will be randomly assigned to breast RT ± regional nodal RT.

We appreciate the importance of the question being asked in these studies and support their conduct. Defining patient subgroups that do (or do not) benefit from our therapies is an important goal. It is possible that response to preoperative chemotherapy predicts for the potential benefit of local regional RT (and hence the associated therapeutic ratio). Responders to preoperative chemotherapy may have a lesser need for additional local regional RT. However, we believe the converse may be true: that the potential survival benefits of local therapies are likely highest among responders to preoperative chemotherapy.

Consider the more typical clinical scenario for node-positive patients who undergo initial mastectomy, followed by adjuvant chemotherapy (Fig 1). In that setting, the addition of PMRT improves overall survival (OS) by approximately 6% to 9%.[6-10] This group includes both responders and nonresponders to chemotherapy, although identification of these subgroups is not possible, because chemotherapy is administered postoperatively. If it is true that responders to neoadjuvant chemotherapy derive lesser survival gains with PMRT, it must follow that nonresponders derive greater gains, because the OS benefit should still be 6% to 9% (ie, sequencing of surgery and chemotherapy should not alter this; Fig 1, lower panel).

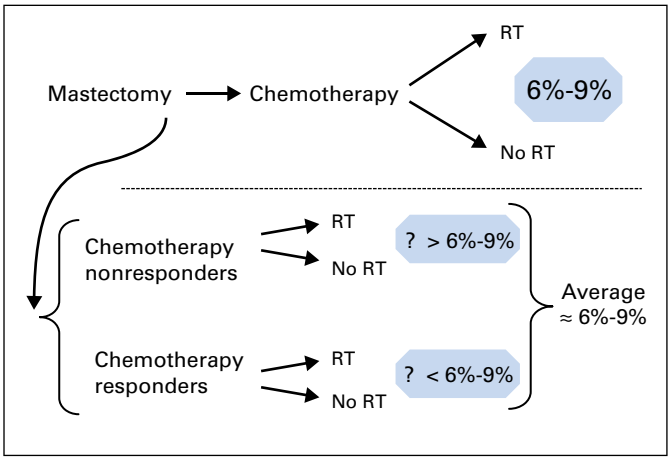

Fig 1. After mastectomy and chemotherapy, the addition of locoregional radiotherapy (RT) improves overall survival by 6% to 9% (upper panel). Among these patients, there are responders and nonresponders to chemotherapy, although we are not able to identify who they are (lower panel). If the survival benefit of RT is reduced in responders (eg, < 6% to 9%), the survival benefit of RT in nonresponders must be > 6% to 9% (because results in the two groups must average to 6% to 9%). The analogous argument can be made for nodal RT in patients undergoing breast-conservation therapy with lumpectomy and chemotherapy.

An analogous situation exists for patients undergoing breast conservation. The NCIC Clinical Trials Group MA.20 study reported improvements in locoregional control and distant disease-free survival and a trend in OS with the addition of nodal RT to breast RT in patients undergoing lumpectomy followed by chemotherapy.[11] If responders to preoperative chemotherapy derive lesser gains with nodal RT, nonresponders should derive greater gains (again, to make the math work). As we discuss here, the evidence suggests that the opposite may be true: namely, that responders to systemic therapy might derive the most survival benefit from RT.

Are there data to support reducing locoregional therapy in patients receiving systemic therapy? Yes, but the data are limited and somewhat conflicting.[5,12] The strongest evidence supporting this approach is from a pooled analysis of all three arms of NSABP B-27 and the preoperative chemotherapy arm of NSABP B-18.[5] In total, 3,088 evaluable patients received preoperative chemotherapy followed by local therapy with either mastectomy (without RT) or lumpectomy and breast RT (without nodal RT). In the subset with clinically positive axillary nodes before chemotherapy, there were no local or regional failures among the 32 patients who received chemotherapy followed by mastectomy, with no evidence of tumor in the breast or nodes; there were only three regional failures among the 230 patients who received chemotherapy followed by lumpectomy and breast RT, with no evidence of tumor in the nodes. Thus, there were few reported failures in anatomic sites with a pathologic complete response to chemotherapy even without RT.

These data are limited by the absence of histologic confirmation of pretreatment lymph nodes status and the relatively small numbers of patients experiencing pathologic complete response. They are further constrained by the problem of assessing locoregional recurrence. Scoring locoregional recurrence can be challenging, particularly in the supraclavicular and internal mammary nodal areas. The NSABP studies typically report only the first sites of failure in their patterns of failure analyses. Patients experiencing simultaneous systemic and local failures are not scored as having local recurrence, even if the persistence of locoregional disease is potentially the source of subsequent systemic relapse. Patients who experience systemic failure usually do not necessarily undergo routine assessments for locoregional recurrence. Conversely, patients who experience locoregional failure do routinely undergo evaluation for systemic recurrence. Therefore, the reported rate of locoregional failure may be understated.

There are data to support caution in reducing local therapy in settings with more effective systemic therapy. In the 2005 EBCTSG (Early Breast Cancer Trialists' Collaborative Group) overview, the addition of PMRT improved OS largely in patients receiving systemic therapy (chemotherapy or tamoxifen) and less so in those patients not receiving systemic therapy (Web Fig 6B in overview by Clarke et al).[6] In other words, as systemic therapies were applied, the addition of local RT was better able to provide OS improvements.

In the 2011 EBCTSG overview, proportional improvements in breast cancer mortality afforded by postlumpectomy RT in women with node-negative, estrogen receptor (ER) –positive tumors were similar among patients receiving and not receiving tamoxifen (event ratio, 0.77 for both groups). The absolute reduction in the annual rate of breast cancer mortality associated with breast RT was 0.3% per year in those receiving tamoxifen versus 0.7% per year in those not receiving tamoxifen (Web Fig 4 in EBCTSG report).[13] Nevertheless, receipt of an active systemic agent (ie, tamoxifen) did not totally negate the suggested benefits in breast cancer mortality from local breast RT. Furthermore, the absolute impact of RT on relapse rates (any site) was actually lower in those patients receiving tamoxifen (absolute reduction, 1.5% per year; 0.9% per year with RT *v* 2.4% per year without RT) than in those not receiving tamoxifen (absolute reduction, 4.7% per year; 3.3% per year with RT *v* 8.0% per year without RT), because tamoxifen reduces relapse rates (Web Fig 4 in EBCTSG report).[13] The ability of breast RT to provide similar improvements in breast cancer mortality, despite a lower impact on relapse rate, suggests that the survival benefits of improved local control with RT may actually be higher in patients receiving effective systemic therapy.

The findings from a reanalysis of 1,000 patients in the DBCG (Danish Breast Cancer Cooperative Group) 82 b and c studies also support the concept that survival yields from improvements in local control might be increased in patients with lower rates of systemic risk.[14] In those studies, patients with T3 tumors and/or involved axillary nodes were randomly assigned to mastectomy ± locoregional RT (chemotherapy or hormonal therapy was administered to pre- and postmenopausal patients, respectively). Among those with the highest risk of systemic spread (based on various unfavorable clinical features, such as $>$ three positive nodes, tumor $>$ 2 cm, ER negativity, human epidermal growth factor receptor 2 [HER2] positivity), an approximate 36% improvement in locoregional control failed to result in any improvement in OS. Among those with an intermediate risk of systemic spread, a 19% improvement in locoregional control was associated with a 9% improvement in OS. Among those with the lowest risk of systemic spread (eg, $\leq$ three nodes, tumor $\leq$ 2 cm, ER positivity, HER2 negativity), an approximate 11% improvement in locoregional control was associated with a 12% trend toward improved OS.[14] Thus, as the risk of systemic disease declined, there was an apparent increasing ability for improvements in local control to improve OS.

The relative utilities of systemic and local therapies with regard to OS depend on the systemic and local disease burdens (which are on a broad continuum) and the ability of the available therapies to sterilize those disease burdens. The theoretic interaction between local and systemic therapies suggests these approaches are synergestic.[15,16] Improvements in local control are unlikely to yield improvements in OS unless systemic disease is either nonexistent or sterilized by systemic therapy. Among patients who harbor micrometastatic disease, as the efficacy of systemic therapy increases, and systemic micrometastatic disease is sterilized, the ability of local therapy to improve survival should generally increase. With further efficacy, systemic therapy can provide both systemic and local control, and the utility of local therapies declines.[15,16]

In settings where there is interpatient variation in the degree of response to systemic therapy, those who respond at the local primary site are likely the subset of patients more likely to have experienced micrometastatic disease sterilization. If some of these patients have a greater tumor burden at the local regional site (*v* systemic sites), adding a locoregional therapy, and not relying only on chemotherapy for local regional control, is appropriate. Reducing locoregional therapy in this subset of patients might be a suboptimal strategy and may result in reduced OS.

A prior study that reduced local therapy based on favorable responses to initial systemic therapy noted an unexpectedly high rate of local failure.[17] However, the patients in that study had more advanced disease than the patients who will be enrolled onto the RTOG/NSABP studies (RTOG/NSABP trial is limited to patients with clinical T1-3 N1 disease). Many of these patients, if they were to undergo initial surgery, would have pathologic T1-2 N1 disease and have a relatively low risk of subsequent locoregional recurrence, even without RT.

RT has risks (eg, pulmonary risks, cardiac risks, lymphedema, secondary malignancies, damage to breast reconstruction). The potential benefits of RT need to be considered in the context of these risks. Care must be taken to minimize the risks and optimize the therapeutic ratio. This becomes increasingly important as the potential benefits in some subgroups might be small, and modest changes in RT technique might significantly increase or decrease the therapeutic ratio.

In summary, studies that consider reductions in local therapies on the basis of good response to systemic therapies should be undertaken with caution and within the confines of a prospective trial. Given this controversy, we certainly support the RTOG/NSABP trial in addressing this important question in a scientific manner. However, we believe the weight of the evidence suggests PMRT and nodal RT in conjunction with breast RT provide the most survival benefits precisely in those patients who are good responders to systemic therapy. Absent participation in a clinical trial, responders to preoperative chemotherapy should generally receive locoregional RT. We might be outsmarting ourselves by continually trying to identify subgroups of patients and individualizing therapy accordingly. Personalized medicine is certainly the current rage, and the attraction of such an approach is self-evident. However, we may be overestimating our knowledge of the underlying biologic realities and excessively relying on imprecise imaging and pathologic assessments. The natural history of breast cancer is long, and differences in OS resulting from changes in locoregional management can take many years to become clinically evident. Time will tell.

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AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

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ORIGINAL REPORT

Patterns of Recurrence After Surgery Alone Versus Preoperative Chemoradiotherapy and Surgery in the CROSS Trials

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See accompanying editorial on page 367

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Clinical trial information: Netherlands Trial Register No. NTR487.

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ABSTRACT

Purpose
To analyze recurrence patterns in patients with cancer of the esophagus or gastroesophageal junction treated with either preoperative chemoradiotherapy (CRT) plus surgery or surgery alone.

Patients and Methods
Recurrence pattern was analyzed in patients from the previously published CROSS I and II trials in relation to radiation target volumes. CRT consisted of five weekly courses of paclitaxel and carboplatin combined with a concurrent radiation dose of 41.4 Gy in 1.8-Gy fractions to the tumor and pathologic lymph nodes with margin.

Results
Of the 422 patients included from 2001 to 2008, 418 were available for analysis. Histology was mostly adenocarcinoma (75%). Of the 374 patients who underwent resection, 86% were allocated to surgery and 92% to CRT plus surgery. On January 1, 2011, after a minimum follow-up of 24 months (median, 45 months), the overall recurrence rate in the surgery arm was 58% versus 35% in the CRT plus surgery arm. Preoperative CRT reduced locoregional recurrence (LRR) from 34% to 14% ($P < .001$) and peritoneal carcinomatosis from 14% to 4% ($P < .001$). There was a small but significant effect on hematogenous dissemination in favor of the CRT group (35% *v* 29%; $P = .025$). LRR occurred in 5% within the target volume, in 2% in the margins, and in 6% outside the radiation target volume. In 1%, the exact site in relation to the target volume was unclear. Only 1% had an isolated infield recurrence after CRT plus surgery.

Conclusion
Preoperative CRT in patients with esophageal cancer reduced LRR and peritoneal carcinomatosis. Recurrence within the radiation target volume occurred in only 5%, mostly combined with outfield failures.

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INTRODUCTION

Patients with esophageal cancer have poor prognosis; at the time of diagnosis; ≥ 50% present with distant metastasis or irresectable disease.[1] For potentially curable patients, for decades, surgical resection had been the main treatment. However, incomplete resections occurred in up to 25%[2] and locoregional recurrence (LRR) in 30% to 40%, with 5-year survival rarely exceeding 25%.[3] Most randomized controlled trials (RCTs) investigating the role of preoperative chemoradiotherapy versus surgery alone failed to show a significant survival benefit, mostly because of a lack of statistical power. However, a recent meta-analysis showed a survival benefit for patients treated with preoperative chemoradiotherapy (CRT) or chemotherapy compared with surgery alone.[4]

The results of the CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) trial have recently been published. This was an RCT comparing preoperative CRT followed by surgery with surgery alone.[5] CRT consisted of 41.4 Gy in 1.8-Gy fractions combined with weekly concurrent carboplatin and paclitaxel. After a minimum follow-up of 24 months, there was a significant estimated 5-year overall survival benefit of 13% in favor of the CRT plus surgery arm. The CRT regimen was well tolerated, with little added toxicity.[5]

Patterns of recurrence of esophageal cancer after surgery compared with CRT plus surgery are

infrequently reported in the literature. Meguid et al[6] and Denham et al[7] describe relapse patterns after CRT plus surgery, and CRT plus surgery and definitive CRT, respectively; however, those patient groups were not compared with surgery alone. Understanding relapse patterns provides insight into the effectiveness of the combined treatment and may lead to improvements. Therefore, we analyzed the recurrence pattern of patients treated in the CROSS trial and the preceding phase II trial investigating the same preoperative regimen.[8] In particular, we related the site of recurrence to the radiation fields employed.

PATIENTS AND METHODS

Patient Population

The patient population consisted of patients enrolled onto the CROSS trial, an RCT in which eligible patients were randomly assigned between CRT plus surgery and surgery alone,[5] and patients included in the preceding phase II trial[8] investigating the same preoperative regimen followed by surgery.

All patients had histologically proven and resectable squamous cell carcinoma (SCC) or adenocarcinoma (AC) of the esophagus, stage cT1N1M0 or cT2-3N0-1M0 according to the Union International Contre Cancer (sixth edition, 2002). The upper border of the tumor had to be $\geq$ 3 cm below the upper esophageal sphincter. Those with tumors of the gastroesophageal junction were also eligible, provided that the primary tumor did not extend $\geq$ 4 cm into the stomach.

Patients had to be age 18 to 75 years with a WHO performance score $\leq$ 2. Weight loss had to be $\leq$ 10%. No past or current history of malignancy other than the entry diagnosis was allowed, except for nonmelanomatous skin cancer, curatively treated carcinoma in situ of the cervix, or a nonrecurred malignancy treated $\geq$ 5 years before enrollment. No previous radiotherapy or chemotherapy was allowed. Written informed consent was required from all patients before random assignment. The medical ethics committees of all eight participating centers approved the study protocol.

Staging

Pretreatment staging included elaborate history taking, physical examination, routine blood workup and pulmonary function tests, an upper GI endoscopy, endoultrasonography, and computed tomography (CT) of neck,

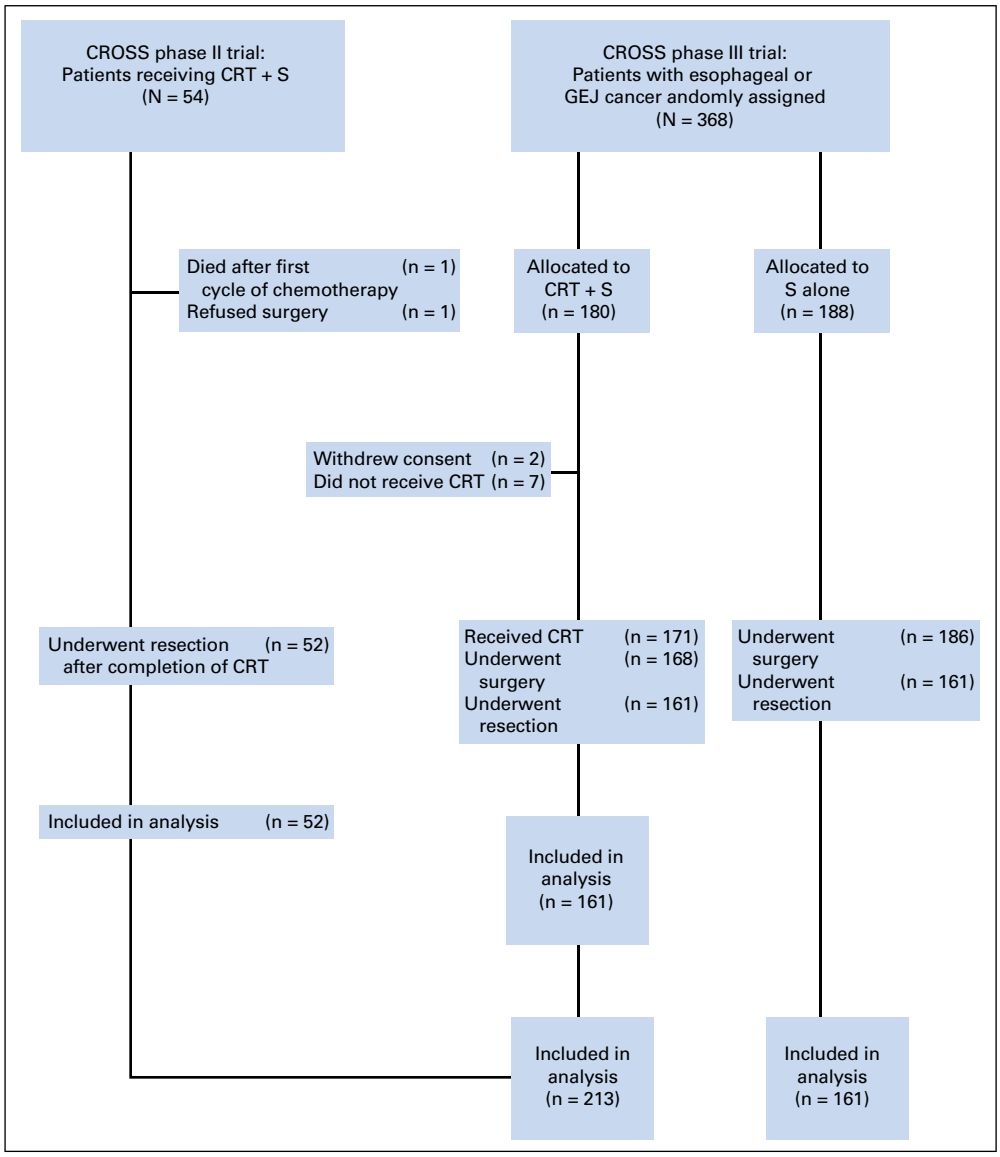

Fig 1. CONSORT diagram. CROSS, Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study; CRT, chemoradiotherapy; GEJ, gastroesophageal junction; S, surgery.

chest, and upper abdomen. On indication, ultrasound of the neck was performed with fine-needle aspiration.

Chemotherapy

Chemotherapy consisted of five cycles of concurrent paclitaxel 50 mg/m^2 and carboplatin targeted at area under the curve of 2, starting on days 1, 8, 15, 22, and 29. Toxicity of CRT was closely monitored using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).[9]

Radiotherapy

A total radiation dose of 41.4 Gy was administered in 23 fractions of 1.8 Gy, five fractions per week, starting on the first day of chemotherapy. All patients were treated with external-beam radiation using a three-dimensional conformal radiation technique. Gross tumor volume was drawn on each relevant slice of the planning CT and was defined by the primary tumor and any enlarged regional lymph nodes. The planning target volume (PTV) provided a proximal and distal margin of 4 cm and a radial margin of 1.5 cm around the gross tumor volume. A distal margin of 3 cm was chosen in case the tumor extended into the gastric cardia. Individually shaped beams were used in each field by either cerrobend blocks or multileaf collimators to ensure optimal sparing of normal tissue. The daily prescription dose of 1.8 Gy was specified at the International Commission on Radiation Units and Measurement 50/62 reference point, and the 95% isodose had to encompass the entire PTV. The maximum dose to the PTV was not to exceed the prescription dose by > 7%. Tissue density inhomogeneity correction was used.

Surgery

Patients randomly assigned to the surgery arm were treated as soon as possible after random assignment. Patients in the CRT plus surgery arm preferably underwent surgery at 6 weeks after completion of CRT; surgery consisted of a transthoracic approach with a two-field lymph node dissection or transhiatal approach, depending on tumor localization,

Table 1. Patient Demographic and Clinical Characteristics at Diagnosis

Characteristic	S Arm (n = 161) No.	%	CRT + S Arm (n = 213) No.	%	P*
Age, years					.54
Median	60		60		
Range	36-73		37-79		
Male sex	129	80	169	81	.85
T stage					
T1	1	1	1	0	.81
T2	35	22	31	15	.12
T3	122	76	180	85	.15
Unknown	1	1	1	0	.40
Nodal stage					
N0	50	31	80	38	.21
N1	106	66	125	61	.22
Unknown	3	3	3	1	.96
Nodal status					
Positive supraclavicular nodes	0	0	0	0	NA
Positive celiac nodes	6	4	8	4	.63
Tumor length, cm					.62
Median	5		5		
Range	1-13		1-12		
Histology					
Adenocarcinoma	122	76	160	75	.87
SCC	38	24	52	24	.88
Other	1	1	1	1	.84

Abbreviations: CRT, chemoradiotherapy; NA, not applicable; S, surgery; SCC, squamous cell carcinoma.
*Analysis of variance test.

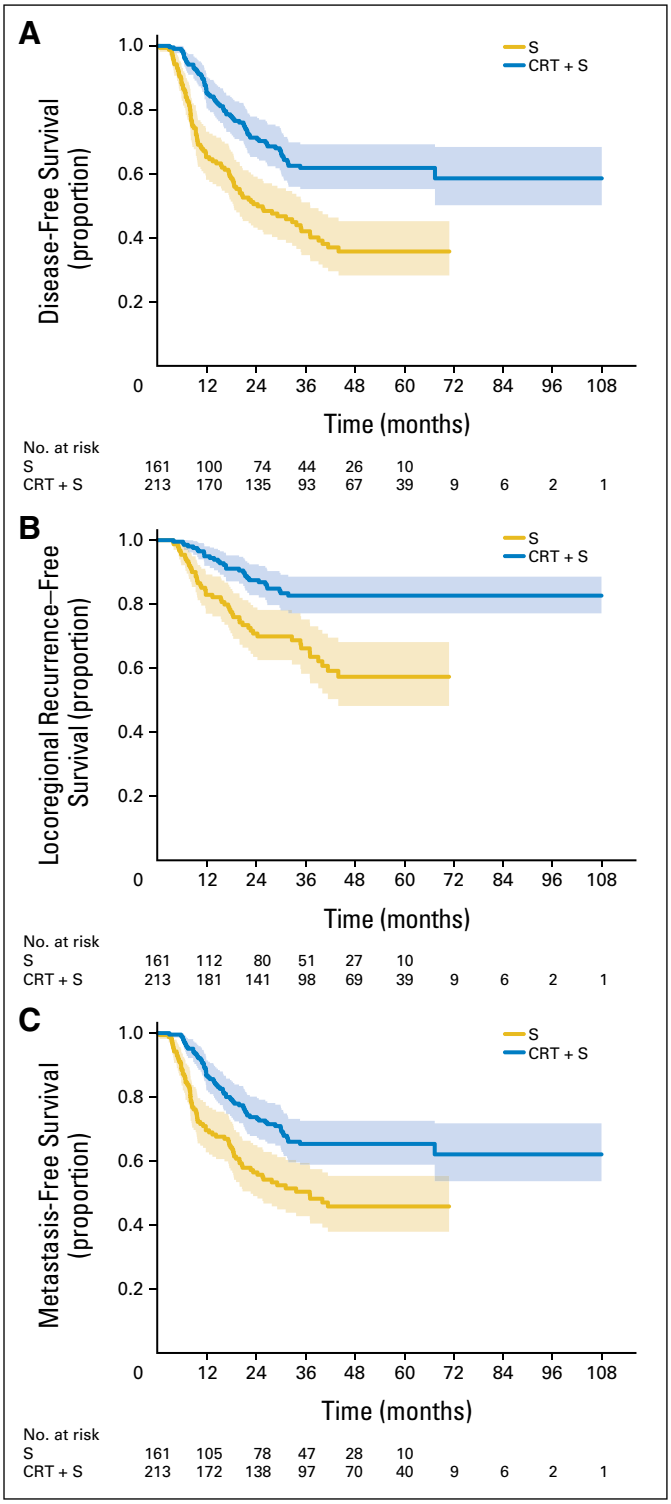

Fig 2. (A) Disease-free survival for patients undergoing surgery alone (S) or chemoradiotherapy (CRT) followed by S (CRT + S; hazard ratio [HR], 0.47; 95% CI, 0.35 to 0.64). (B) Locoregional recurrence–free survival; recurrences at anastomotic site, mediastinum, celiac trunk, or supraclavicular lymph nodes (HR, 0.37; 95% CI, 0.23 to 0.59). (C) Distant metastasis–free survival; systemic metastases including nodal metastases other than regional, peritoneal deposits, and malignant pleural effusion (HR, 0.52; 95% CI, 0.38 to 0.73).

patient characteristics, and local expertise. A wide local excision of the N1 lymph nodes, including standard excision of the celiac nodes, was carried out in both techniques. Continuity of the digestive tract was restored by gastric tube reconstruction or colonic interposition procedure with cervical anastomosis.

Pathologic Analysis

For grading of the therapy response, the degree of histomorphologic regression was classified into four modified categories, as first described by Mandard et al.[10] All resection margins, including circumferential margins, were evaluated for vital tumor, with a cutoff point of 1 mm. If vital tumor was present at ≤ 1 mm from a resection margin, that margin was considered to be positive.

Follow-Up

In the first year after completion of the protocol, patients were seen every 3 months. In the second year, follow-up took place every 6 months and, thereafter, yearly until 5 years after treatment. If applicable, late toxic effects and recurrence of disease or death were documented. During follow-up, additional diagnostics were only performed on indication.

Recurrences

Relapses were classified as locoregional or distant. LRRs were defined as recurrences at the site of the primary tumor or locoregional lymph nodes. Lymph node recurrences at the celiac trunk or in the supraclavicular region were also considered to be locoregional. Distant recurrences were defined as nonregional lymph node recurrences, systemic metastases, malignant pleural effusions, or peritoneal metastases. Most patients suspected of experiencing recurrence underwent a CT scan of thorax and abdomen or an endoscopy. If necessary, cytology or histology was obtained. If a second recurrence was detected within 4 weeks after the first occurrence, it was considered to be synchronous. Localization and date of identification of all locoregional and distant recurrences were scored.

Radiation Target Volumes

In patients with recurrent disease who were treated with CRT plus surgery, radiation target volumes were analyzed in relation to the site of recurrence. Treatment failures were classified as infield when relapse occurred within the PTV, outfield when relapse occurred outside the PTV, and borderline when adjacent to the PTV or field edge. We compared the exact site of recurrence with the treatment volume on the planning CT scan. When a recurrence was detected endoscopically, the location was compared with the results of the staging endoscopy. In case of a relapse at the anastomotic site, endoscopy results, histology reports of the esophageal resection specimen, and planning CT scans were used to reconstruct the proximal and distal ends of the resection specimen in relation to the irradiated volume.

Statistical Analysis

Duration of follow-up was defined as the interval between the day of random assignment and death or the last date of hospital visit or telephone call. The Kaplan-Meier method was used to calculate survival probabilities. The influence of prognostic factors was analyzed using univariable and multivariable Cox regression analyses. The backward-step method was used to optimize the multivariable model. A univariable Cox regression model was also used to analyze the difference per treatment arm for each separate location of recurrence. We used one-way analysis of variance test to investigate the differences between both treatment arms. Analyses were performed using SPSS software (version 18.0; SPSS, Chicago, IL) and the R statistical program (http://www.r-project.org).

RESULTS

Patients

A total of 422 patients were included in both trials (Fig 1). Of the 368 patients in the phase III CROSS trial, two patients were ineligible: one because of withdrawal, and one because of distant metastases at the time of diagnosis. Of the remaining 366 patients, 188 were randomly assigned to the surgery arm and 178 to the CRT plus surgery arm. Of the 54 patients included in the phase II trial, 52 completed the protocol, one patient died after the first course of chemotherapy (probably because of cardiac arrest), and one patient refused surgery after CRT. The 52 patients who underwent resection were included in the analysis of the CRT plus surgery arm. Finally, 418 patients were available for analysis.

All staging was performed before any treatment. Mean age at time of diagnosis was 60 years (range, 36 to 79 years). Male sex and adenocarcinoma were predominant. Of all patients, 78%, 84%, and 90% had a cT3 tumor in the surgery arm, CRT plus surgery arm, and phase II study, respectively. After combining the patients in the phase II trial and CRT plus surgery arm in the phase III CROSS trial, according to the one-way ANOVA test, no significant differences were found between both arms (Table 1).

In the surgery arm, 161 (85.6%) of 188 patients underwent an esophageal resection versus 213 (92.2%) of 230 in the CRT plus surgery group. A microscopically radical (R0) resection was achieved in 68% of patients in the surgery arm and in 93% of patients in the CRT plus surgery arm. In the CRT plus surgery arm, 28% had a pathologic complete response (ypT0N0). One or more pathologically positive lymph nodes were found in 74% of patients in the surgery arm and in 31% of those in the CRT plus surgery arm ($P < .001$).

Patterns of Recurrence

After a minimum follow-up of 24 months and a median survival of 45 months for surviving patients, 57.1% of the resected patients in the surgery group had recurrent disease versus 34.7% in

Table 2. Results of Univariable Cox Regression Analysis of RFS Time per Treatment Arm in Patients Undergoing Resection (n = 374)

	S Arm (n = 161)		CRT + S Arm (n = 213)				
Site of Recurrence	No.	%	No.	%	HR	95% CI	*P*
Anastomosis	14	8.7	6	2.8	0.28	0.11 to 0.72	**.008**
Mediastinum	33	20.5	15	7.0	0.29	0.16 to 0.53	**< .001**
Supraclavicular	7	4.3	9	4.2	0.83	0.31 to 2.2	.71
Celiac axis	11	6.9	8	3.8	0.42	0.17 to 1.04	.06
Para-aortic	17	10.6	14	6.6	0.53	0.26 to 1.1	.08
Peritoneal carcinomatosis	22	13.7	9	4.2	0.27	0.12 to 0.58	**.01**
Hematogenous	57	35.4	61	28.6	0.67	0.46 to 0.96	**.03**

NOTE. Bold font indicates significance.
Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; RFS, recurrence-free survival; S, surgery.

Table 3. Tumor Recurrences in Relation to Radiation Target Volumes in Patients Undergoing CRT Plus Surgery (n = 213)

Recurrence	Infield	Outfield	Borderline	Unknown	Total
LRR only	2	2	2	1	7
Distant only	0	43	0	1	44
LRR plus distant	9	11	3	0	23
Total	11	56	5	2	74

Abbreviations: CRT, chemoradiotherapy; LRR, locoregional recurrence.

the CRT plus surgery group. Most patients had distant failure (22%) or combined locoregional and distant failure (16.5%). Only 9.3% of patients in the surgery arm had an isolated LRR without distant metastasis versus 3.3% in the CRT plus surgery arm. Also, 24.2% versus 10.8% of patients in the surgery and CRT plus surgery arms, respectively, had concurrent locoregional and distant relapses, and 23.6% versus 20.7% of patients had distant relapse only in the surgery and CRT plus surgery arms, respectively. The majority of LRRs occurred within 2 years of follow-up. In the CRT plus surgery arm, no LRRs were observed after 30 months. Figures 2A, 2B, and 2C show the differences between both arms for disease-free survival (DFS), locoregional DFS, and distant metastasis–free survival, respectively.

Site of Recurrence

Further analysis showed that recurrences at the anastomosis occurred in 8.7% versus 2.8% ($P = .008$) of patients in the surgery and CRT plus surgery arms, respectively (Table 2). LRRs at the anastomosis occurred more often after R1 resections (11%) than after R0 resections (4%) and more often in patients with pN1 disease (7%) than in those with pN0 disease (3%). Mediastinal relapses occurred in 20.5% versus 7.0% ($P < .001$) of patients in the surgery and CRT plus surgery arms, respectively. Peritoneal carcinomatosis occurred in 13.7% versus 4.2% ($P < .001$) of patients and hematogenous metastasis occurred in 35.4% versus 28.6% ($P = .025$) of patients in the surgery and CRT plus surgery arms, respectively. There were no significant differences between both arms in recurrence rates at the supraclavicular or celiac axis levels (Table 2). Generally, these latter areas were not included in the radiation target volume.

Site of Recurrence in Relation to the Radiation Target Volume

In the 74 patients with recurrences after CRT plus surgery, the precise localization of relapse was determined and correlated to the irradiated field volume (Table 3). Infield recurrences occurred in 11 (5.2%) of 213 patients, of whom only two patients experienced an infield recurrence without synchronous distant failure. Recurrences at the borders of the treatment volume occurred in five (2.3%) of 213 patients; three of these occurred at the site of the celiac axis. In two of the borderline recurrences, the site of relapse was in the anterior-posterior beams but not in the lateral beams. Regional outfield recurrences occurred in 13 (6.1%) of 213 patients; two of these were solitary LRRs. Two patients were scored as unknown; one had a relapse at the site of the anastomosis, and for the other, the diagnostic CT scan of the recurrence could not be retrieved.

Potential Prognostic Factors for Developing an LRR

Table 4 lists the results of the analyses per treatment arm. Prognostic factors predicting LRRs in univariable analysis were surgery alone, pathologically positive lymph nodes (pN1), and R1 resection. In the multivariable analysis, the backward method showed that surgery alone, pathologic nodal stage N1, and histology of SCC significantly increased the risk of developing an LRR. After multivariable analysis, surgery alone, pN1, and SCC remained independent prognostic factors.

In the surgery arm, 47% of patients with SCC developed an LRR compared with 30% of patients with AC. In the CRT plus surgery arm, there was no significant difference between SCC and AC (15% and 14%, respectively).

Of the 59 patients with a pathologic complete response (pCR) after CRT, 17% developed any recurrent disease; only one patient (1.7%) had a solitary LRR. Of the 154 patients with no pCR, 42% experienced a recurrence: LRR ± distant recurrence in 17% and a solitary LRR in 4%. After R1 resection, there was no significant difference in LRRs between treatment arms, although a trend was present (36% *v* 29% for surgery and CRT plus surgery, respectively).

Table 4. Univariable and Multivariable Cox Regression Analyses for LRRs in Patients Undergoing Resection (n = 374)

	LRR Incidence (%)		Univariable		Multivariable	
Factor	S Arm	CRT + S Arm	HR	95% CI	HR	95% CI
Method of resection (TTE *v* THE)	20 *v* 17	6 *v* 8	0.83	0.54 to 1.29	NA	
Tumor length (≤ 5.0 *v* > 5.0 cm)	23 *v* 39	16 *v* 11	0.89	0.54 to 1.46	NA	
Clinical T stage (T1-2 *v* T3-4)	31 *v* 35	5 *v* 17	1.32	0.76 to 2.29	NA	
Clinical nodal stage (N0 *v* N1)	31 *v* 35	10 *v* 18	1.50	0.93 to 2.41	NA	
Pathologic nodal stage (N0 *v* N1)	22 *v* 38	10 *v* 23	**3.66**	**2.2 to 5.85**	**2.85**	**1.59 to 5.11**
Involved margins (R0 *v* R1)	34 *v* 36	13 *v* 29	**2.29**	**1.38 to 3.76**	NA	
Histology (SCC *v* AC)	47 *v* 30	15 *v* 14	0.70	0.44 to 1.12	**0.49**	**0.29 to 0.82**
Sex (male *v* female)	33 *v* 34	12 *v* 20	1.12	0.67 to 1.87	NA	
Treatment arm (S *v* CRT + S)	27	14	**0.37**	**0.23 to 0.59**	**0.50**	**0.29 to 0.86**
pCR after CRT (no *v* yes)*	NA	7 *v* 17	0.36	0.13 to 1.05	NA	

NOTE. Bold font indicates significance.
Abbreviations: AC, adenocarcinoma; CRT, chemoradiotherapy; HR, hazard ratio; LRR, locoregional recurrence; NA, not applicable; pCR, pathologic complete response; S, surgery; SCC, squamous cell carcinoma; THE, transhiatal esophagectomy; TTE, transthoracic esophagectomy.
*Factor only available in the CRT + S arm and therefore not suitable for multivariable analysis.

DISCUSSION

In the CROSS phase III trial, preoperative CRT followed by surgery compared with surgery alone improved DFS, with an absolute difference of 22% at 5 years and an improved overall survival of 13%. Most patients diagnosed with LRRs also developed synchronous distant metastases. Of the patients undergoing resection, 24% and 11% had concurrent LRRs and distant relapses and only 9.3% and 3.3% had an isolated LRR in the surgery and CRT plus surgery arms, respectively. Few data are available on relapse patterns after CRT plus surgery for esophageal and gastroesophageal cancers. In most RCTs comparing CRT plus surgery with surgery alone, the sites of recurrence are either imprecise or not reported. LRR rates of 13% to 25% and 12% to 42% after CRT plus surgery and surgery alone, respectively, have been reported.[11-13] Most studies have shown a reduction in LRRs after preoperative CRT.[11,13]

In our study, patients with a pCR after CRT had a significantly lower LRR rate compared with patients with a partial (tumor regression grade 2 to 3) or no response after CRT (tumor regression grade 4 to 5). Of patients with a pCR, 17% had recurrent disease, of whom only one patient had a solitary LRR. The only patient experiencing LRR after pCR had no lymph nodes examined in the resection specimen and should probably be considered as having experienced inadequately staged pCR. These data compare favorably with those of Meguid et al,[6] who in their retrospective series reported five solitary infield recurrences in 82 patients (6%) achieving pCR after CRT.

A marked difference was seen in the occurrence of peritoneal carcinomatosis in favor of the CRT plus surgery arm (13.7% *v* 4.2%; $P < .001$). This might be explained by a reduction of microscopic residual disease, because of patients achieving pCR, 1.7% had peritoneal metastasis compared with 5.2% with no pCR. The reduction in recurrences at the site of anastomosis in the CRT arm might be an effect of a reduction of microscopically positive surgical margins. Unfortunately, in case of R1 resection, the site of irradicality was not always reported. This is supposedly more likely at the lateral borders of the specimen than at the cranial or caudal borders. Irradicality and subsequent tumor spill could also be considered a cause of recurrence at the anastomosis or in the abdominal cavity.

In both the multivariable and univariable analyses, patients with SCC had a higher probability of developing LRR; however, this was significant only in the multivariable analysis. Patients with SCC are known to have a higher risk of LRR after surgery alone,[14] which is confirmed by the current data. Of patients with SCC undergoing resection in the surgery arm, 47% experienced LRRs compared with 30% of those with AC. However, because SCC histology has a higher response rate to CRT, this was not a prognostic factor in the univariable analysis. After CRT, there was no difference between SCC and AC regarding LRR. Therefore, in the surgery arm, histology was an independent negative prognostic factor for LRR, which disappeared after preoperative CRT.

Recurrences of only 5% within the radiation target volumes confirms the hypothesis that preoperative CRT reduces the LRR rate. Recurrences at the supraclavicular fossae, generally not included in the radiation target volumes of midesophageal and distal tumors, were similar in both groups (4%), which further confirms this conclusion. Huang et al[15] described supraclavicular lymph node recurrences in 16.7% of 54 patients with SCC of the proximal esophagus after surgery alone, which included removal of pathologic supraclavicular lymph nodes. In the small group of patients with proximal tumors, no supraclavicular recurrences were seen, probably because of the proximity of the supraclavicular fossae to the radiation treatment volume.

Of the 20 patients with a recurrence near the celiac axis, 18 had a primary tumor located in the distal esophagus, and most of them had synchronous distant metastases. On the basis of these data, elective inclusion in the radiation target volume of the supraclavicular fossae for mid or distally located tumors or celiac nodes for mid or proximal tumors would probably not have a large effect on survival. The idea behind preoperative CRT in the treatment of esophageal cancer and cancer of the gastroesophageal junction was to improve survival by reducing locoregional failure. However, we also observed a small but significant effect on the development of hematogenous metastasis. From the current data, it cannot be concluded whether this was a systemic effect of the chemotherapy or an indirect effect of reducing LRRs. However, the short interval and frequently occurring synchronous recurrences argue in favor of the first hypothesis.

In conclusion, preoperative CRT in patients with esopheageal or junctional cancer improves locoregional control and has an effect on both hematogenous metastasis and peritoneal carcinomatosis. A pCR after CRT was a favorable prognostic factor for both locoregional and systemic recurrences.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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ORIGINAL REPORT

Concomitant Cisplatin Plus Radiotherapy and High–Dose-Rate Brachytherapy Versus Radiotherapy Alone for Stage IIIB Epidermoid Cervical Cancer: A Randomized Controlled Trial

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ABSTRACT

Purpose
The benefits of chemoradiotherapy (CRT) for cervical cancer compared with radiation (RT) alone seem to diminish in later-stage disease. However, these modalities have not been directly compared for disease-free interval (DFI) and overall survival (OS) of women with stage IIIB cervical cancer.

Patients and Methods
We conducted a randomized controlled clinical trial comparing DFI and OS of 147 women with stage IIIB squamous cervical cancer who received either cisplatin plus RT (CRT) or RT alone (72 patients in the CRT group and 75 patients in the RT-only group).

Results
The CRT group had significantly better DFI (hazard ratio [HR], 0.52; 95% CI, 0.29 to 0.93; $P = .02$). However, patients in the CRT group did not have significantly better OS than those in the RT-only group (HR, 0.67; 95% CI, 0.38 to 1.17; $P = .16$). Toxicity was graded according to criteria of the Radiation Therapy Oncology Group. The organs affected (excluding hematologic effects) did not differ significantly between groups. Also, late toxicity events and organs affected were not significantly disproportionate between the study groups.

Conclusion
For stage IIIB cervical cancer, the addition of cisplatin offers a small but significant benefit in DFI, with acceptable toxicity.

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INTRODUCTION

The last decade of the twentieth century witnessed a major improvement in the treatment of cervical cancer as the benefits of chemoradiotherapy (CRT) over radiotherapy (RT) alone were then unequivocally demonstrated.[1] Data from five well-designed and properly performed phase III trials showed a 30% to 50% reduction in risk of death in women receiving combination treatments. These pioneer studies, however, although conducted in countries with low incidence of advanced and bulky disease, did not address use of combined modalities of treatment for women with advanced locoregional disease.[2-6]

Currently available data comparing treatment modalities are derived from studies that assessed patients with stage I to IVB disease.[3,4,7-13] Because most studies were performed in geographic regions with low incidence of advanced and bulky disease, the data available for treatment comparisons in patients with advanced disease are not as robust as those for patients with early-stage disease. Until now, the best evidence available comparing disease-free interval (DFI) and overall survival (OS) of women receiving CRT versus RT alone is summarized in a meta-analysis of 18 trials.[14] This meta-analysis concluded that CRT may benefit women with all stages of cervical cancer, although the size of the benefit may vary across staging strata. The benefit of CRT decreased from 10% for women with stage IB to IIA cervical cancer to 3% for women with stage III to IVA cancer. In the subset of women with stage III to IVA cancer, the CIs of the hazard ratios (HRs) comparing DFI and OS were not significant. Also notably, the meta-analysis recognized that serious acute toxicity related to chemotherapy was measured only in a few of the eligible trials.

None of these trials addressed relative toxicity and results of concomitant cisplatin and high–dose-rate brachytherapy. Here, we present the results of a randomized controlled trial, the primary end point of which was 5-year DFI of women with stage IIIB squamous cell cervical cancer who received either RT alone or CRT, associated with high–dose-rate brachytherapy.

PATIENTS AND METHODS

Study Design

This was a randomized controlled clinical trial comparing, as primary end points, the DFI and OS (disease related) of women with stage IIIB squamous cervical cancer receiving cisplatin plus RT (CRT) or RT alone. Patients and caregivers were not blinded to the treatment options.

Random Assignment Procedure

A random assignment schedule was produced using the SAS statistical package (SAS Institute, Cary, NC). Allocation was concealed using opaque envelopes.

Selection of Patients

This study was conducted in the RT clinics of the Women's Hospital, State University of Campinas (São Paulo, Brazil). The study was approved by the Institutional Review Board on April 8, 2003, and by the local Research Ethics Committee on September 16, 2003 (Protocol No. 238/2003). All patients who met the inclusion criteria and who signed the informed consent form were invited to enroll. Accrual lasted from September 2003 through July 2010. Follow-up lasted through June 2013. Inclusion criteria included the following: stage IIIB squamous cell carcinoma of cervix, as ascertained by an experienced gynecologic oncologist and a radiation oncologist (baseline work-up consisted of a complete pelvic exam, cystoscopy, retrosigmoidoscopy, chest x-ray, and pelvic and abdominal ultrasounds); creatinine clearance more than 60 mL/min/1.73 m^2; liver enzymes in the normal range; Karnofsky performance status more than 70%; and baseline hemoglobin levels $\geq$ 10 mg/dL.

Clinical and Biologic Characteristics

Baseline and follow-up data were recorded in specialized forms designed for the study. After checking for inclusion criteria, patients were approached by one of the investigators (A.C.Z.O.) and invited to enroll. Those who accepted were interviewed regarding key clinical and epidemiologic features. Next, treatment was performed, and treatment data were recorded. Follow-up visits were scheduled 1 month after treatment and then every 4 months for the next 2 years, every 6 months through the third year, and annually thereafter. Follow-up visits consisted essentially of the same procedures performed at the baseline visit, with the addition of cervical cytology and exclusion of routine cystoscopy and retrosigmoidoscopy, unless otherwise indicated.

Description of Treatment Modalities

For patients in either the CRT or RT-only group, external-beam RT was delivered with anteroposterior and posteroanterior opposed beams of 10-MV photons if the patient's pelvic anteroposterior diameter was $\leq$ 17 cm or using four fields (anteroposterior, posteroanterior, and two lateral fields) if it was more than 17 cm. The treatment field extended from the space between L4 and L5 to the midpubis or to a line 4 cm below the most distal vaginal or cervical site of disease. Lateral fields were designed to encompass S3 posteriorly, with a margin of at least 3 cm from the primary cervical tumor. The RT dose was keyed to the central ray at the patient's midplane (for anteroposterior-posteroanterior fields) or to the isocenter of the beams, calculated by a software planning system. The total dose to be delivered to the pelvis was 45 Gy, at 1.8 Gy per fraction of RT. Patients in the CRT group also received concomitant weekly cisplatin (40 mg/m^2) during the pelvic external-beam RT.

Statistical Analysis

All statistical analyses were performed with the R Project for Statistical Computing (http://www.r-project.org/). $P = .05$ was considered significant; CIs were set at 95%. Sample size calculations were based on estimates of cumulative rate of disease-free survival at 5 years of 60% in the CRT group and 40% in the RT-only group. These parameters were obtained from reports available in 2002 to 2003 when the study was conceived.[3] The postulated HR used was 0.50. However, actual data showed a much less unbalanced frequency of death events between groups. Post hoc analyses using the following parameters shows that a sample size of 71 patients on each arm is sufficient for the conclusions pertaining to DFI in our study: 80% power; $\alpha = .05$; 56% treatment failure rate in controls; 62% treatment failure rate in patient cases; 1:1 treatment allocation; and a postulated HR = 0.53. We had 147 patients in follow-up (72 patients in the CRT group and 75 patients iin the RT-only group), and a median follow-up period of 43.2 months (defined as median time at risk for all patients; ie, follow-up of a given patient is the time elapsed between treatment and death or censoring). χ^2 and Fisher's exact tests were used to assess the balance of clinical and epidemiologic variables between the two study groups. Multivariable Cox proportional hazards models were used to calculate the hazard ratios for OS and disease-specific survival (defined as time elapsed between start of treatment and death from any cause and time elapsed between start of treatment and disease-related death, respectively) and DFI (defined as the time elapsed between treatment start and recurrence), in relation to the key clinical features of the patients and the study group allocation. Finally, we produced Kaplan-Meier survival curves comparing the 5-year OS and DFI of the two study arms.

RESULTS

Table 1 lists the clinical characteristics of patients with stage IIIB cervical cancer treated in the CRT or RT-only arms. Figure 1 shows

Table 1. Clinical Characteristics of the Study Patients

Clinical Characteristic	Study Group: CRT No. of Patients	CRT %	RT Only No. of Patients	RT Only %	*P**
Age, years					.37
≥ 45	47	66	55	74	
< 45	24	34	19	26	
Karnofsky performance status					.46
≥ 90%	54	83	52	76	
< 90%	11	17	16	24	
Parametrial invasion					.07
Unilateral	4	6	12	16	
Bilateral	68	94	61	84	
Parametria invaded to the pelvic wall					.94
No	27	37	28	38	
Yes	45	63	45	62	
Vaginal invasion					.72
No/proximal	64	90	68	93	
Distal	7	10	5	7	
Baseline hemoglobin, mg/dL					.56
≥ 10	59	83	65	88	
< 10	12	17	9	12	
Tumor grade					.93
1-2	55	77	58	79	
3	16	23	15	21	

Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy.
*χ^2 tests were used to calculate *P* values. Fisher's exact test was used when n ≤ 5.

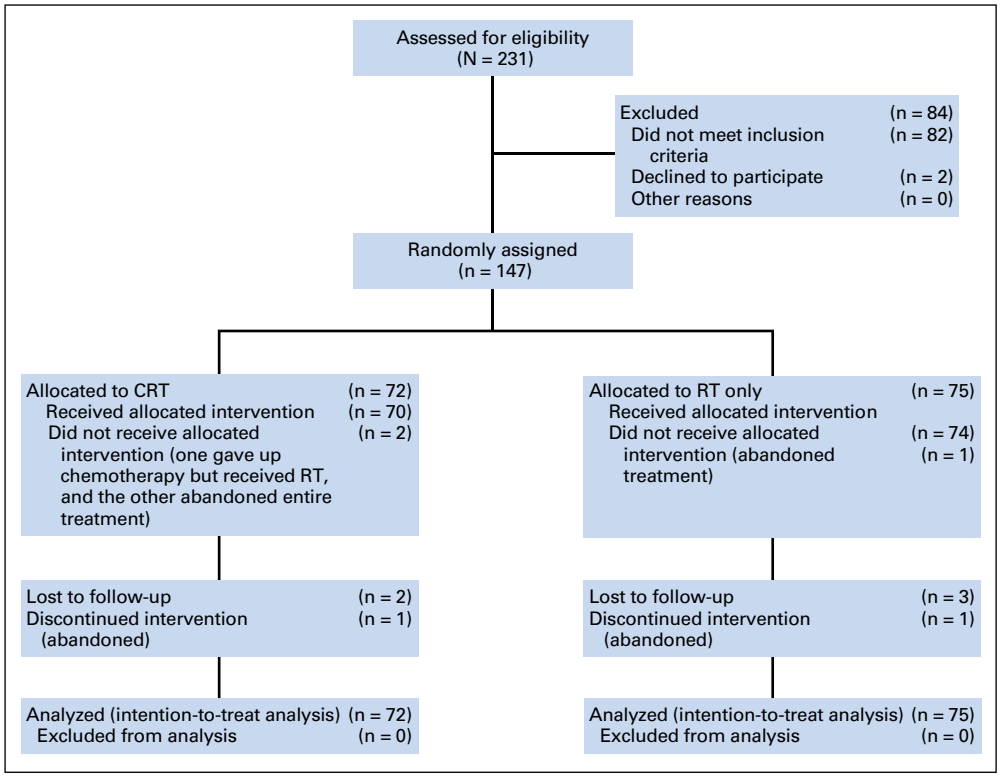

Fig 1. CONSORT diagram. CRT, chemoradiotherapy; RT, radiotherapy.

the CONSORT diagram. Univariable comparisons of these features show that the study groups were balanced with regard to patient age, Karnofsky status, laterality and extent of parametrial and vaginal invasion, baseline hemoglobin concentration, tumor grade, and initial response to treatment. Median follow-up time was 42.3 months (50% central range, 28.8 to 63.1 months) for the CRT group and 43.3 months (50% central range, 21.2 to 65.0 months) for the RT-only group (data not shown).

Toxicity was graded according to criteria of the Radiation Therapy Oncology Group.[15] Events occurring in the CRT and RT-only groups are listed in Table 2. Grade 1 to 2 acute toxicity was diagnosed in 27 patients (37.5%) in the CRT group and 21 patients (28%) in the RT-only group ($P = .29$). The organs affected (excluding hematologic effects) did not differ significantly between groups (P values calculated for each non–mutually exclusive event; all nonsignificant). In addition, late toxicity events ($P = .29$) and organs affected (P values for each organ) were not significantly disproportionate between the study groups.

Table 3 lists patient outcomes by the end of follow-up. Forty-three patients (59.7%) in the CRT group and 40 patients (53.3%) in the RT-only group were alive at the end of follow-up. Only four of 43 patients in the CRT group and three of 40 patients in the RT-only group had detectable disease by the end of the follow-up. Twenty-nine patients (40.3%) in the CRT group and 35 patients (46.6%) in the RT-only group died. The proportions of women who died of recurrent disease, their recurrence sites, and other causes of death did not differ significantly between the study groups.

Table 4 lists the DFI, disease-specific survival, and OS profiles according to the clinical characteristics of the patients and study group allocation. Patients with baseline Karnofsky performance status of less than 90% had a significantly worse DFI (HR, 2.73; 95% CI, 1.47 to 5.07; $P < .01$). The same was true for patients with bilateral wall invasion (HR, 2.98; 95% CI, 1.45 to 6.12; $P < .01$) and mean levels of hemoglobin less than 10 mg/dL during treatment (HR, 2.47; 95% CI, 1.24 to 4.92; $P = .01$). Women allocated to the CRT group had significantly better DFI (HR, 0.52; 95% CI, 0.29 to 0.93; $P = .02$). The disease-specific survival was also negatively associated with the following patient characteristics: baseline Karnofsky performance status less than 90% (HR, 2.67; 95% CI, 1.44 to 4.97; $P < .01$), bilateral parametrial wall invasion (HR, 2.27; 95% CI, 1.12 to 4.60; $P = .02$), and mean hemoglobin less than 10 mg/dL (HR, 2.38; 95% CI, 1.20 to 4.72; $P = .01$). Patients allocated to the CRT group did not have a significantly better disease-specific survival (HR, 0.61; 95% CI, 0.34 to 1.09; $P = .09$) compared with women in the RT-only group. OS was negatively associated with the following patient characteristics: baseline Karnofsky performance status less than 90% (HR, 2.37; 95% CI, 1.29 to 4.33; $P < .01$) and mean hemoglobin less than 10 mg/dL during treatment (HR, 2.29; 95% CI, 1.17 to 4.49; $P = .01$). Patients allocated to the CRT group did not have a significantly better OS (HR, 0.67; 95% CI. 0.38 to 1.17; $P = .16$) compared with women in the RT-only group. (See Statistical Analysis in Patients and Methods for clarification on the study power–related disease-specific and OS differences.)

Figure 2 shows Kaplan-Meier DFI and OS curves by treatment allocation. The probability of being disease free after 3 years was 66% (95% CI, 56% to 78%) for the CRT group and 55% (95% CI, 44% to 67%) for the RT-only group; at 5 years, it was 61% (95% CI, 50% to 74%) for the CRT group and 51% (95% CI, 40% to 64%)

Table 2. Comparison of Acute and Late Toxicity Events

Toxicity	CRT No. of Patients	CRT %	RT Only No. of Patients	RT Only %	*P**
Acute toxicity					.29
Absent	45	62.5	54	72	
Grades 1-2	26	36.1	21	28	
Grade 5	1†	1.4	0		
Acute toxicity by organ‡					
GI	12	30.8	12	42.9	.91
Bladder	13	33.3	15	53.6	.74
Vagina	4	10.3	1	3.6	.20
Hematologic	10	25.6	0	0.0	—§
Late toxicity					.29
Absent	44	61.1	48	64.0	
Grades 1-2	21	29.2	24	32.0	
Grades 3-4	7	9.7	3	4.0	
Grade 5	0		1‖		
Late toxicity organs‡					
GI	21	58.3	22	68.8	.98
Bladder	9	25.0	7	21.9	.53
Vagina	6	16.7	3	9.4	.32

NOTE. Toxicity was graded according to the Radiation Therapy Oncology Group criteria.[15]

Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy.

*χ^2 tests were used to calculate *P* values. Fisher's exact test was used when $n \leq 5$.

†Pancytopenia.

‡Because these events are not mutually exclusive, *P* values were calculated for each event or organ affected.

§Hematologic toxicity was not considered in statistical comparisons.

‖Intestinal toxicity.

Table 3. Status of Patients at the End of the Follow-Up Period

Status	CRT No. of Patients	CRT %	RT Only No. of Patients	RT Only %
Alive	43	59.7	40	53.3
Alive without disease	39	54	37	49.3
Alive with disease	4	5.5	3	4
Recurrence site				
Local	3		2	
Lymphatic	1		1	
Distant	2		1	
Deaths	29	40.3	35	46.6
Death as a result of recurrence	25	34.7	32	42.6
Type of recurrence in women who died as result of disease				
Local	16		18	
Lymphatic	10		17	
Distant	15		17	
Other causes of death	4		3	
Death as a result of treatment toxicity	1		1	
Acute myocardial infarction	1		1	
Pneumonia	1		0	
Congestive cardiac failure	1		0	
Chronic obstructive pulmonary disease	0		1	

Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy.

for the RT-only group. The probability of being alive after 3 years (considering death from any cause) was 68% (95% CI, 58% to 80%) for the CRT group compared with 64% (95% CI, 54% to 76%) for the RT-only group; after 5 years, the probability of being alive was 56% (95% CI, 45% to 70%) for the CRT group and 54% (95% CI, 43% to 67%) for the RT-only group.

DISCUSSION

Although the superiority of combined CRT over RT alone in the treatment of cervical cancer is sufficiently well established to be reflected in current practice guidelines,[2-7] the superior results of CRT seem to dim as disease stage advances (ie, for the subset of women with stage III or greater cervical cancer, the advantages of the combined treatments have not been unequivocally demonstrated). This knowledge gap led us to design the present trial, which, to our knowledge, is the first randomized controlled trial specifically designed to address the outcomes of patients with stage IIIB cervical cancer receiving CRT with high-dose RT versus RT alone. Our results demonstrate that a better DFI can be expected for women receiving combined treatment. However, because of sample size limitations, a benefit in OS could not be demonstrated.

CRT is thought to exert its beneficial effects by improving control of local disease. Lethality in patients with stage IIIB disease is a result of locally recurring disease in a large proportion of the patients, but death as a result of distant metastases is not negligible.[16-18] In our study, of the 64 women who died, 57 (89%) died of recurrent disease; of these 58 patients, 32 had distant metastases. A meta-analysis of 18 trials from 11 countries recently suggested that CRT may also have an effect on time to metastasis, which may be considered as a beneficial systemic effect.[14] Notably, however, this benefit has been demonstrated in trials encompassing a broad spectrum of disease stages, with relatively small subsets of women with stage IIIB disease.[1,14] In our study, the percentages of patients who experienced recurrence in the two study arms were statistically similar, and disease-specific survival was not related to treatment arm. Although incidence of distant metastasis in the CRT arm was numerically smaller than that in the RT-only arm, this difference was not statistically significant and did not translate into an up-front OS benefit. We acknowledge, however, that sample size limitations of our study preclude adequate analysis of the subset of women with distant metastases. Another limitation of our study is the lack of a straightforward and systematic diagnosis of hydronephrosis, which precludes the use of this clinical feature as a control variable in the survival models.

In addition to sample size limitations in stage IIIB patient subsets in most studies comparing CRT and RT alone for treatment of cervical cancer, many other technical dissimilarities between studies may hamper the comparison of their results. Chemotherapy scheduling and type, RT dose, brachytherapy regimen (either high or low dose), and overall treatment duration vary widely among trials.[14,19] We decided on the treatment modalities to be used in this study based on literature available in 2002 to 2003, but current treatment options do not differ substantially from those available at the time the study was designed.

Table 4. Disease-Free Interval, Overall Survival, and Disease-Specific Survival According to Key Clinical Characteristics and Study Group Allocation

Factor	Disease-Free Interval			Disease-Specific Survival*			Overall Survival*		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age: ≥ *v* < 45 years	1.29	0.70 to 2.39	.40	1.24	0.65 to 2.35	.50	1.06	0.57 to 1.99	.83
Karnofsky performance status: ≥ *v* < 90%	2.73	1.47 to 5.07	< .01	2.67	1.44 to 4.97	< .01	2.37	1.29 to 4.33	< .01
Parametrial invasion to the pelvic wall: unilateral *v* bilateral	2.98	1.45 to 6.12	< .01	2.27	1.12 to 4.60	.02	1.72	0.92 to 3.24	.08
Mean hemoglobin levels during treatment†: ≥ *v* < 10 mg/dL	2.47	1.24 to 4.92	.01	2.38	1.20 to 4.72	.01	2.29	1.17 to 4.49	.01
Tumor grade: 1-2 *v* 3	0.71	0.35 to 1.44	.35	0.99	0.51 to 1.90	.98	1.11	0.60 to 2.05	.72
Study group allocation: RT only *v* CRT	0.52	0.29 to 0.93	.02	0.61	0.34 to 1.09	.09	0.67	0.38 to 1.17	.16

NOTE. Multivariable Cox proportional hazards regressions were used.
Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; RT, radiotherapy.
*Only deaths related to cervical cancer were considered.
†As assessed before concentrated RBC transfusion. Transfusions were prescribed when indicated, before resuming RT.

Our study treatment regimens were based on high–dose-rate brachytherapy. Our concerns over treatment choice have now been dissipated, as a recent meta-analysis compared high–dose-rate and low–dose-rate brachytherapy as treatment modalities for patients with intracavity locally advanced cervical cancer. This analysis of four studies with a total of 1,265 women showed no differences in OS, DFI, local control rates, recurrence, and metastasis for stages I, II, and III cervical cancer in patients receiving either high– or low–dose-rate brachytherapy.[19]

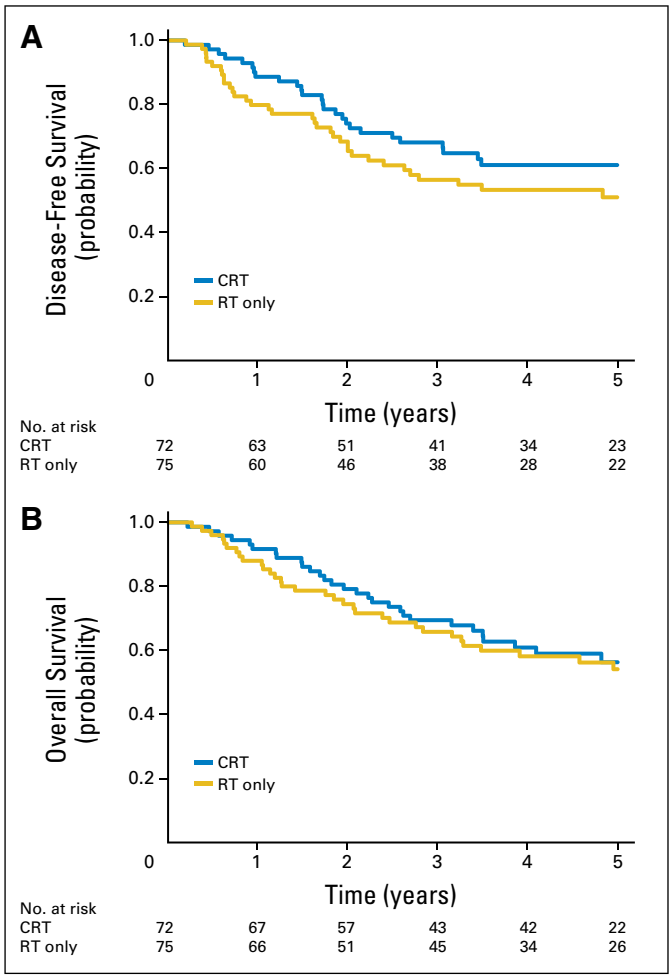

Fig 2. (A) Disease-free survival and (B) overall survival curves for the chemoradiotherapy (CRT) and radiotherapy (RT) only treatment groups.

In our study, toxicity profiles of the CRT and RT-only protocols were comparable. All randomized clinical studies with solid evaluations of treatment toxicity used low–dose-rate brachytherapy; however, we know of no randomized clinical trial published to date that assesses toxicity associated with chemotherapy and high–dose-rate brachytherapy; studies that make this evaluation are restricted to case reports[20-23] or nonrandomized controlled trials,[24,25] with divergent results. Although the association has been reported to show increased toxicity,[20] or even a prohibitive toxicity profile,[26] these findings have not yet been replicated elsewhere. A recent meta-analysis comparing low– and high–dose-rate brachytherapy indicated that high–dose-rate brachytherapy has an acceptable toxicity profile, except in regard to complications of the small intestine.[19]

Our results suggest that CRT results in better DFI in patients with stage IIIB cervical cancer than does RT alone. However, we were unable to detect a better OS associated with CRT, possibly because of the size of this study. This trial was not powered enough for OS evaluation, even though it was intended to be at its design. These results are in accord with other non–advanced-stage focused trials and meta-analyses.[8-14] Notably, the addition of chemotherapy has not significantly increased the toxicity of RT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Antonio Carlos Zuliani, Sergio Carlos Barros Esteves, Luiz Carlos Teixeira, Júlio César Teixeira, Gustavo Antonio de Souza
Collection and assembly of data: Antonio Carlos Zuliani
Data analysis and interpretation: Antonio Carlos Zuliani, Luis Otávio Sarian
Manuscript writing: All authors
Final approval of manuscript: All authors

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ORIGINAL REPORT

Burnout and Career Satisfaction Among US Oncologists

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ABSTRACT

Purpose
To evaluate the personal and professional characteristics associated with career satisfaction and burnout among US oncologists.

Methods
Between October 2012 and March 2013, the American Society of Clinical Oncology conducted a survey of US oncologists evaluating burnout and career satisfaction. The survey sample included equal numbers of men and women and represented all career stages.

Results
Of 2,998 oncologists contacted, 1,490 (49.7%) returned surveys (median age of respondents, 52 years; 49.6% women). Among the 1,117 oncologists (37.3% of overall sample) who completed full-length surveys, 377 (33.8%) were in academic practice (AP) and 482 (43.2%) in private practice (PP), with the remainder in other settings. Oncologists worked an average of 57.6 hours per week (AP, 58.6 hours per week; PP, 62.9 hours per week) and saw a mean of 52 outpatients per week. Overall, 484 oncologists (44.7%) were burned out on the emotional exhaustion and/or depersonalization domain of Maslach Burnout Inventory (AP, 45.9%; PP, 50.5%; $P = .18$). Hours per week devoted to direct patient care was the dominant professional predictor of burnout for both PP and AP oncologists on univariable and multivariable analyses. Although a majority of oncologists were satisfied with their career (82.5%) and specialty (80.4%) choices, both measures of career satisfaction were lower for those in PP relative to AP (all $P < .006$).

Conclusion
Overall career satisfaction is high among US oncologists, albeit lower for those in PP relative to AP. Burnout rates among oncologists seem similar to those described in recent studies of US physicians in general. Those oncologists who devote the greatest amount of their professional time to patient care seem to be at greatest risk for burnout.

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INTRODUCTION

Although rewarding, caring for patients with cancer is demanding and stressful.[1] Oncologists work long hours, supervise the administration of highly toxic therapy, and are continually exposed to death and suffering.[1-3] These characteristics place oncologists at risk for burnout, a syndrome characterized by emotional exhaustion, treating people as if they are objects (ie, depersonalization), and loss of meaning or purpose in work.[1,4] In addition to potentially profound personal consequences (eg, anxiety, depression, alcohol/substance use, suicide),[5-8] burnout among physicians seems to have important professional consequences, including adverse effects on quality of care and professionalism.[9-13] Studies also suggest that physicians experiencing burnout are more likely to reduce their work hours and/or pursue early retirement,[14] with potential manpower implications for the physician workforce. Although isolated studies have explored burnout in national samples of US oncologists (most recently in 2003),[15,16] little is known about personal and professional characteristics associated with burnout and professional satisfaction.[1,17,18]

METHODS

Participants

A sample of 3,000 oncologists was assembled from the 8,998 US oncologists in the American Society of Clinical Oncology (ASCO; Alexandria, VA) membership file. To ensure adequate representation of oncologists at different career stages and of both sexes, oncologists in the membership file were classified by sex and categorized into three groups according to years in practice (< 10, 10 to 19, and > 20 years). Oncologists were then selected at random to construct a sample evenly distributed by career stage (n = 1,000 from each of career stage category) and sex (1,500 men; 1,500 women).

Table 1. Personal Characteristics for Oncologists in AP Versus PP

Characteristic	All (N = 1,117)		AP (n = 377)		PP* (n = 482)		P†
	No.	%	No.	%	No.	%	
Age, years							
Median	52		50		52		.0037
Missing	32		10		12		.0380
< 40	63	5.8	29	7.9	24	5.1	
40-49	369	34.0	150	40.9	161	34.3	
50-59	343	31.6	113	30.8	165	35.1	
≥ 60	310	28.6	75	20.4	120	25.5	
Sex							< .001
Missing	18		5		3		
Male	554	50.4	158	42.5	260	54.3	
Female	545	49.6	214	57.5	219	45.7	
Children							< .001
Missing	17		4		3		
Yes	946	86.0	299	80.2	431	90.0	
No	154	14.0	74	19.8	48	10.0	
Youngest child age, years							.0532
Missing	173		79		51		
< 5	119	12.6	55	18.5	47	10.9	
5-12	249	26.4	85	28.5	121	28.1	
13-18	159	16.8	51	17.1	83	19.3	
19-22	106	11.2	34	11.4	53	12.3	
> 22	311	32.9	73	24.5	127	29.5	
Relationship status							.1721
Missing	16		3		3		
Single	98	8.9	40	10.7	32	6.7	
Married	949	86.2	317	84.8	427	89.1	
Partnered	34	3.1	12	3.2	12	2.5	
Widowed/widower	20	1.8	5	1.3	8	1.7	
Ever gone through divorce							.1962
Missing	20		6		5		
Yes	193	17.6	60	16.2	79	16.6	
No	896	81.7	310	83.6	391	82.0	
Currently going through one	8	0.7	1	0.3	7	1.5	
Current student loan debt							.0742
Missing	19		2		6		
No debt	985	89.7	324	86.4	432	90.8	
Debt < $25,000	26	2.4	13	3.5	9	1.9	
$25,000-$49,999	13	1.2	9	2.4	2	0.4	
$50,000-$74,999	28	2.6	14	3.7	11	2.3	
$75,000-$99,999	16	1.5	6	1.6	8	1.7	
$100,000-$125,000	10	0.9	2	0.5	6	1.3	
> $125,000	20	1.8	7	1.9	8	1.7	

Abbreviations: AP, academic practice; PP, private practice.
*Including single-specialty group, multispecialty group, and health maintenance organization.
†AP to PP.

The 3,000 individuals in the sample were sent an e-mail stating the purpose of the study (eg, to better understand factors contributing to career satisfaction among US oncologists) and providing a link to an electronic survey in October 2012. Three reminder requests were sent over the ensuing 3 weeks. Two individuals sent surveys were deceased, yielding a final sample of 2,998. Individuals not responding to the electronic survey were mailed an identical paper version of the survey in November 2012. Those not responding by January 2013 were sent a brief postcard survey. As an incentive to participate, oncologists who completed the full-length survey received a free ASCO educational product. Participation was voluntary, and all data were deidentified before analysis. ASCO commissioned the study with human subject oversight provided by the Institutional Review Board of the Mayo Clinic (Scottsdale, AZ).

Study Measures

Full-length survey. The full-length survey included 60 questions exploring a variety of personal and professional characteristics and using standardized instruments to measure burnout and career satisfaction. The full survey is available by request.

Burnout was measured using the Maslach Burnout Inventory (MBI), a 22-item questionnaire considered the gold-standard tool for measuring burnout.[4,19-21] The MBI has three subscales to evaluate each domain of burnout: emotional exhaustion, depersonalization, and low personal accomplishment. In the standard scoring for health care workers, physicians with scores ≥ 27 on the emotional exhaustion subscale, ≥ 10 on the depersonalization subscale, or < 33 on the personal accomplishment subscale are considered to have a high degree of burnout in that dimension.[4] In keeping with previous

Table 2. Practice Characteristics for AA Versus PP

Characteristics	All (N = 1,117)		AP (n = 377)		PP* (n = 482)		*P*†
	No.	%	No.	%	No.	%	
Years in practice‡							
Mean	21.7		19.4		21.0		.0262
Median	20.0		18.0		20.0		
< 10	148	14.5	64	18.7	62	13.9	.0599
10-19	337	33.1	126	36.8	152	34.0	
≥ 20	533	52.4	152	44.4	233	52.1	
Practice setting							
Academic medical center	377	34.0	377		—		
PP single-specialty group	335	30.2	—		335	69.5	
PP multispecialty group	124	11.2	—		124	25.7	
PP health maintenance organization	23	2.1	—		23	4.8	
Veterans hospital	20	1.8	—		—		
Active military practice	2	0.2	—		—		
Industry	59	5.3	—		—		
Not in practice or retired	31	2.8	—		—		
Other	138	12.4	—		—		
Time devoted to patient care, %							< .001
Missing	10		1		2		
None	82	7.5	3	.8	1	0.2	
1-25	94	8.6	43	11.4	8	1.7	
26-50	121	11.0	99	26.3	7	1.5	
51-75	199	18.0	140	37.2	39	8.1	
76-100	611	55.2	91	24.2	425	88.5	
Focus on specific type cancer							< .001
Missing	45		11		16		
Yes	418	39.0	295	80.6	81	17.4	
No	654	61.0	71	19.4	385	82.6	
Time supervising physicians in training, %							< .001
Missing	78		25		25		
0	385	37.1	9	2.6	241	52.7	
< 5	232	22.3	48	13.6	141	30.9	
5-10	183	17.6	103	29.3	56	12.3	
11-20	130	12.5	106	30.1	12	2.6	
> 20	109	10.5	86	24.4	7	1.5	
Hours and call schedule							
Median nights on call/week	1		1		2		< .001
Hours seeing patients at work/week							< .001
Mean	34.0		29.2		43.4		
SD	17.2		14.1		11.9		
Hours on administrative tasks at work/week							< .001
Mean	11.5		14.6		8.9		
SD	10.5		11.0		6.9		
Hours spent at home on work tasks/week							< .001
Mean	8.5		10.8		7.2		
SD	8.7		8.5		7.2		
Hours at home to keep abreast of developments/week							.4064
Mean	4.6		4.6		4.3		
SD	4.0		3.8		3.3		
Mean total hours/week§							< .001
Median	57.6		58.6		62.9		
SD	20.8		17.7		16.2		
Outpatient practice							
Outpatients in clinic/week							< .001
Mean	51.7		37.4		74.2		
SD	34.6		21.0		31.0		
Minutes allocated/new outpatient							.0011
Mean	49.1		53.9		51.5		
SD	20.3		17.0		14.8		
Minutes allocated/return outpatient							< .001
Mean	18.2		20.7		17.8		
SD	8.2		6.8		6.1		

(continued on following page)

Table 2. Practice Characteristics for AA Versus PP (continued)

Characteristics	All (N = 1,117)		AP (n = 377)		PP* (n = 482)		P†
	No.	%	No.	%	No.	%	
Hospital practice							
Hospital rounding							< .001
Missing	45		5		18		
Round own patients when hospitalized	162	15.1	20	5.4	118	25.4	
Share rounding with partners in blocks	171	16.0	58	15.6	92	19.8	
Share rounding with partners on weekends	307	28.6	35	9.4	218	47.0	
Attend oncology teaching service	249	23.2	224	6.2	7	1.5	
Do not round in hospital	183	17.1	35	9.4	29	6.3	
No. of inpatients on average hospital day							< .001
Mean	7.0		11.9		5.1		
SD	7.3		8.1		5.3		
No. of weekends rounding in hospital/year							< .001
Mean	9.8		7.2		13.0		
SD	9.8		5.5		10.9		
Compensation method							< .001
Missing	102		25		26		
Salary no incentive	336	33.1	134	38.1	95	20.8	
Salary with bonus	466	45.9	207	58.8	182	39.9	
Pure incentive	213	21.0	11	3.1	179	39.3	

Abbreviations: AP, academic practice; PP, private practice; SD, standard deviation.
*Including single-specialty group, multispecialty group, and health maintenance organization.
†Comparison of AP to PP.
‡Since completion of fellowship training.
§Sum of above four categories.

studies[22-24] and convention,[25] we considered physicians with high scores on the depersonalization and/or emotional exhaustion subscales as having at least one manifestation of professional burnout.[4] Career satisfaction was assessed using two questions from previous physician surveys regarding career and specialty choice.[17,23,26-29]

Postcard survey. To gain insight into participation bias, oncologists not completing the full-length survey were sent a six-question postcard survey that collected information on age, sex, years in practice, and career satisfaction, along with a validated two-item measure of burnout shown to be an accurate proxy measure of burnout.[30-32]

Statistical Analysis

All full-length and postcard surveys received by March 15, 2013, were included in the analysis. Standard descriptive statistics were used to characterize responding oncologists. Associations between variables were evaluated using the Kruskal-Wallis (continuous variables) or χ^2 test (categorical variables) as appropriate. All tests were two sided with type I error rates of 0.05. With the 1,117 responses to the full-length survey, the percentage estimates are accurate to 2.9% with 95% confidence. Comparisons between men and women oncologists were tested using Wilcoxon-Mann-Whitney and Fisher's exact tests. Comparisons with 554 men and 545 women have 80% power to detect an average difference of 17% times the standard deviation, a relatively small effect size.[33,34] Multivariable analysis to identify demographic and professional characteristics associated with the dependent outcomes was performed using logistic regression (Appendix, online only). All analyses used SAS software (version 9; SAS Institute, Cary, NC).

RESULTS

Personal and Professional Characteristics

Of 2,998 oncologists who received an invitation to participate, 1,490 (49.7%) responded. Of these, 1,117 oncologists (75.0%) completed the full-length survey (613 electronic; 504 paper version), and 373 (25.0%) completed postcard surveys. Participants were representative of the overall sample with respect to sex; however, early-career oncologists (in practice < 10 years) were somewhat less likely to respond than later-career oncologists (in practice ≥ 20 years). Comparison of full-length survey responders with those completing only the postcard survey (a standard approach for evaluating response bias) did not identify any statistically significant differences with respect to age, sex, years in practice, or satisfaction with specialty choice (Appendix Table A1, online only). Validated single-item measures[34,35] of the emotional exhaustion or depersonalization domains of burnout[30,31] also failed to identify significant differences. Subsequent analysis focused on participants completing full-length surveys.

The median age of participants was 52 years, with approximately 40% of participants younger than age 50 years (Table 1). Participants were evenly divided by sex. A majority of oncologists (86.2%) were currently married. Independent of relationship status, 86.0% of oncologists reported having children, and nearly half of these oncologists (527; 47.2.%) had a child age ≤ 18 years (ie, school age).

With respect to practice setting (Table 2), most oncologists were in private practice (PP; 43.2%) or academic practice (AP; 33.8%), with smaller proportions working at a veterans' hospital, in active military practice, or in other settings. Of the 482 oncologists in PP, 335 (69.5%) were in a single-specialty practice, 124 (25.7.%) a multispecialty practice, and 23 (4.8%) a health maintenance organization (HMO).

Oncologists spent 57.6 hours per week devoted to professional activities, including an average of 34.0 hours per week on direct patient care, 11.5 hours per week on administrative tasks at work, and 8.5 hours per week performing work tasks at home (completing paperwork, preparing talks, writing grants/manuscripts, and so on), plus 4.6 hours per week keeping abreast of developments in the field and

maintenance of certification. On average, oncologists cared for 52 patients in the outpatient setting each week.

Comparison of PP and AP

Extensive differences in both demographic and practice characteristics were observed between PP and AP oncologists (Tables 1 and 2). Oncologists working in AP settings were slightly younger (median age, 50 *v* 52 years; $P = .0037$), more likely to be women (57.5% *v* 45.7%; $P < .001$), and less likely to have children (80.2% *v* 90.0%; $P < .001$). On average, oncologists in AP worked 4.3 fewer hours each week (58.6 *v* 62.9 hours; $P < .001$) and devoted less professional effort to direct patient care, with 38.5% in AP spending ≤ 50% of their effort on patient care compared with 3.4% in PP. Oncologists in AP were more likely to focus on treating patients with one specific type of cancer (80.6% *v* 17.4%; $P < .001$) and spent a greater proportion of their time supervising physicians in training.

Oncologists in PP saw nearly twice as many patients each week, on average, as those in AP (74.2 *v* 37.4; $P < .001$). Despite the difference in the total number of patients seen per week, the amount of time allocated for each new patient (PP, 52 minutes; AP, 54 minutes; $P = .0011$) and return patient (PP, 18 minutes; AP, 21 minutes; $P < .001$) differed only slightly. The relationship between the number of patients seen per week and percentage of professional effort devoted to clinical care and the number of hours devoted to patient care each week is shown in Figures 1A and 1B.

The method of compensation differed for AP compared with PP, with a larger proportion of PP oncologists in a purely incentive-based model (PP, 39.3% *v* AP, 3.1%; $P < .001$) and fewer in a salary-only (PP, 20.8% *v* AP, 38.1%; $P < .001$) or salary–plus–productivity bonus model (PP, 39.9% *v* AP, 58.8%; $P < .001$). PP oncologists were more likely to report a > 10% decline in compensation in 2012 relative to 2011 (PP, 35.2% *v* AP, 8.0%; $P < .001$). Other differences between PP and AP are summarized in Table 2. A subanalysis of PP oncologists according to practice setting (ie, single specialty, multispecialty, HMO) can be found in Appendix Tables A2 and A3 (online only).

Oncologist Well-Being

Table 3 summarizes burnout, fatigue, and career satisfaction among participating oncologists. When assessed using the full MBI, 38.3% of oncologists had high emotional exhaustion, 24.9% had high depersonalization, and 13.2% had a low sense of personal accomplishment. In aggregate, 44.7% of oncologists had at least one symptom of burnout (high emotional exhaustion score and/or high depersonalization). Demographic characteristics associated with burnout on univariable analysis included younger age, being a woman, relationship status, not having children, and greater student loan debt (Appendix Table A4, online only). Professional characteristics associated with burnout on univariable analysis (Appendix Table A5, online only) included hours worked per week, number of hours spent seeing patients per week (Figs 2A and 2B), devoting more time to patient care, seeing a larger number of patients per week, and method of compensation (burnout rates: salary only, 40.7%; salary with bonus, 47.1%; pure incentive, 53.8%; $P = .011$). Although oncologists in PP had higher median emotional exhaustion and depersonalization scores than did those in AP, no difference in the overall burnout rate was observed by practice setting (PP, 50.5% *v* AP, 45.9%; $P = .177$). A subanalysis of well-being among PP oncologists based on practice setting can be found in Appendix Table A6 (online only).

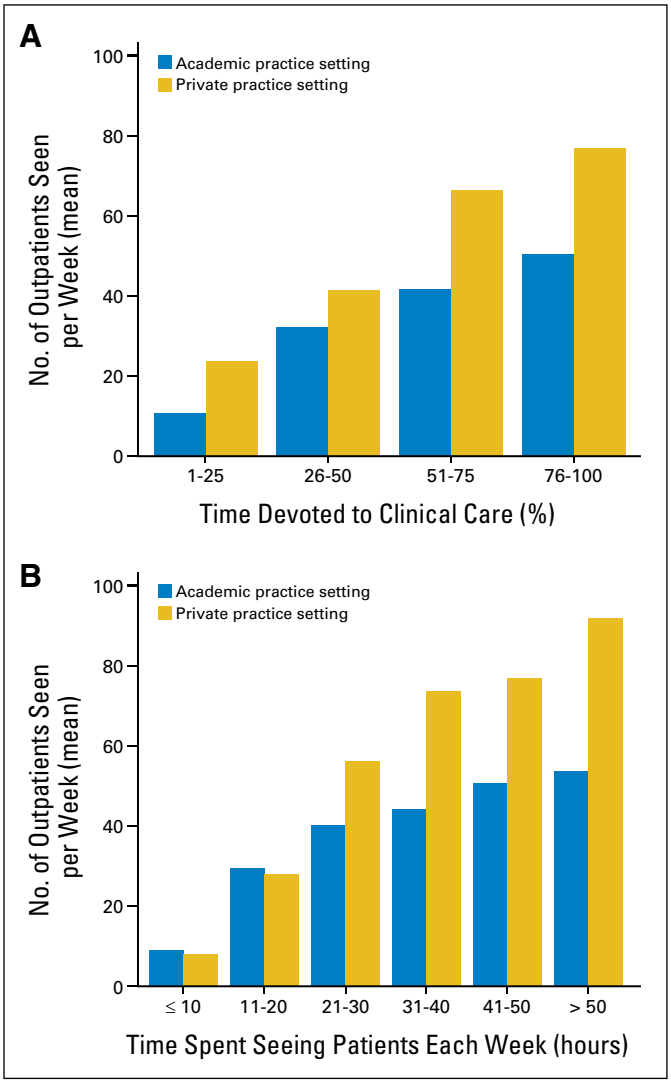

Fig 1. Hours and effort devoted to clinical care and patients seen per week. The relationship between the number of outpatients seen per week (*y*-axis) and (A) percentage of effort devoted to clinical care or (B) hours spent seeing patients each week on *x*-axis.

A majority of oncologists indicated they would choose to become a physician (82.5%) and oncologist (80.5%) again if they could revisit their career and specialty choices. Career satisfaction, as measured by these items, was higher for oncologists in AP than PP (Table 3).

Multivariable Analysis

We performed multivariable analysis to identify personal and professional characteristics associated with burnout and career satisfaction. In addition to an overall model, separate models were developed by practice setting because of the profound differences in personal and professional characteristics of oncologists in PP and AP (Table 4). Younger age and greater number of hours spent seeing patients each week were independently associated with burnout in all models. Each year older reduced the risk of burnout by approximately 4% to 5% (eg, 10 years older, 40% to 50% lower risk), whereas each additional hour spent seeing patients each week increased the risk of burnout by approximately 2% to 4% (eg, 20% to 40% higher risk for

Table 3. Career Satisfaction and Burnout

Characteristic	All (N = 1,117)		AP (n = 377)		PP (n = 482)		
	No.	%	No.	%	No.	%	*P*
Burnout indices*							
Emotional exhaustion†							
Median	22		22		24		.0895
Low score	433	40.1	146	39.0	157	33.0	.1798
Intermediate score	233	21.6	78	20.9	113	23.7	
High score	413	38.3	150	40.1	206	43.3	
Depersonalization†							
Median	5		5		6		.0124
Low score	558	52.3	191	51.3	220	46.1	.0165
Intermediate score	243	22.8	99	26.6	110	23.1	
High score	265	24.9	82	22.0	147	30.8	
Personal accomplishment							
Median	42		41		42		.0415
High score	660	63.0	225	61.0	304	64.0	.3109
Intermediate score	249	23.8	89	24.1	117	24.6	
Low score‡	138	13.2	55	14.9	54	11.4	
Burned out§	484	44.7	172	45.9	241	50.5	.1769
Career satisfaction							
Would become physician again (career choice)	908	82.5	328	87.5	378	79.2	.0016
Would become oncologist again (specialty choice)	877	80.5	314	85.1	368	77.5	.0053

Abbreviations: AP, academic practice; MBI, Maslach Burnout Inventory; PP, private practice.
*As assessed using the full MBI.
†Per the standard scoring of the MBI for health care workers, physicians with scores ≥ 27 on the emotional exhaustion subscale, ≥ 10 on the depersonalization subscale, or < 33 on the personal accomplishment subscale are considered to have a high degree of burnout in that dimension.
‡Low scores on the personal accomplishment subscale are less favorable.
§High score on emotional exhaustion and/or depersonalization subscales of the MBI (see Methods).

each additional 10 hours). In the overall model, each additional hour per week spent on work-related tasks while at home also increased the risk of burnout by approximately 2% (eg, 10% higher risk for each additional 5 hours per week), and focusing on a specific type of cancer increased the risk of burnout by approximately 40%.

Risks specific to practice setting were also observed. Having children was associated with an approximately 55% decreased risk of burnout among PP oncologists (odds ratio [OR], 0.45) but was not a significant factor for oncologists in AP. In contrast, being a woman was associated with an approximately 65% increased risk of burnout among oncologists in AP (OR, 1.68) but was not a significant factor for oncologists in PP. Each additional hour per week spent on administrative tasks at work increased risk of burnout by approximately 5% among PP oncologists (eg, 5 more hours per week, approximately 25% higher risk), whereas each additional hour per week spent on work tasks at home increased risk by approximately 3.5% among AP oncologists (eg, 5 more hours per week, approximately 17.5% higher risk). Among AP oncologists, focusing on one type of cancer was associated with an increased risk of burnout of 320% (OR, 3.24). For those in AP, having less time allocated for each return patient visit (return slots of 20 minutes in length had a 36% increased risk of burnout compared with return slots of 30 minutes in length) and each additional weekend on call per year also increased risk of burnout.

DISCUSSION

This is the first national study of US oncologists evaluating burnout and career satisfaction to our knowledge since 2003 and is the only national study to our knowledge to evaluate burnout in US oncologists using standardized instruments. Approximately 45% of oncologists had at least one symptom of burnout at the time of the survey. Although burnout was strongly related to a variety of personal characteristics on univariate analysis, younger age was the only demographic factor independently associated with risk on multivariable analysis adjusting for professional characteristics. In contrast, a variety of professional characteristics were independently associated with burnout. Hours per week devoted to direct patient care was the dominant professional factor associated with burnout. The number of hours per week spent performing work tasks at home and focusing clinical practice on a specific type of cancer were also independently associated with burnout risk.

The strong, incremental relationship between time devoted to patient care and burnout is concerning, especially given the projected shortage in the supply of oncologists during the coming decades. Medical oncologists already work more hours than physicians in most other disciplines.[35] Reducing clinical work hours or the volume of patients seen may be a strategy to decrease burnout for individual oncologists but at the societal level could exacerbate the projected oncologist workforce shortage.[1,14] The findings also suggest that productivity-based compensation models designed to increase the volume of care oncologists provide are associated with higher burnout and may be self-defeating in the long run.

Although the qualitative differences in AP and PP are recognized, the data collected here provide granular information about these differences and explore associations with burnout and career satisfaction. Oncologists in AP were younger, more likely to be women, and less

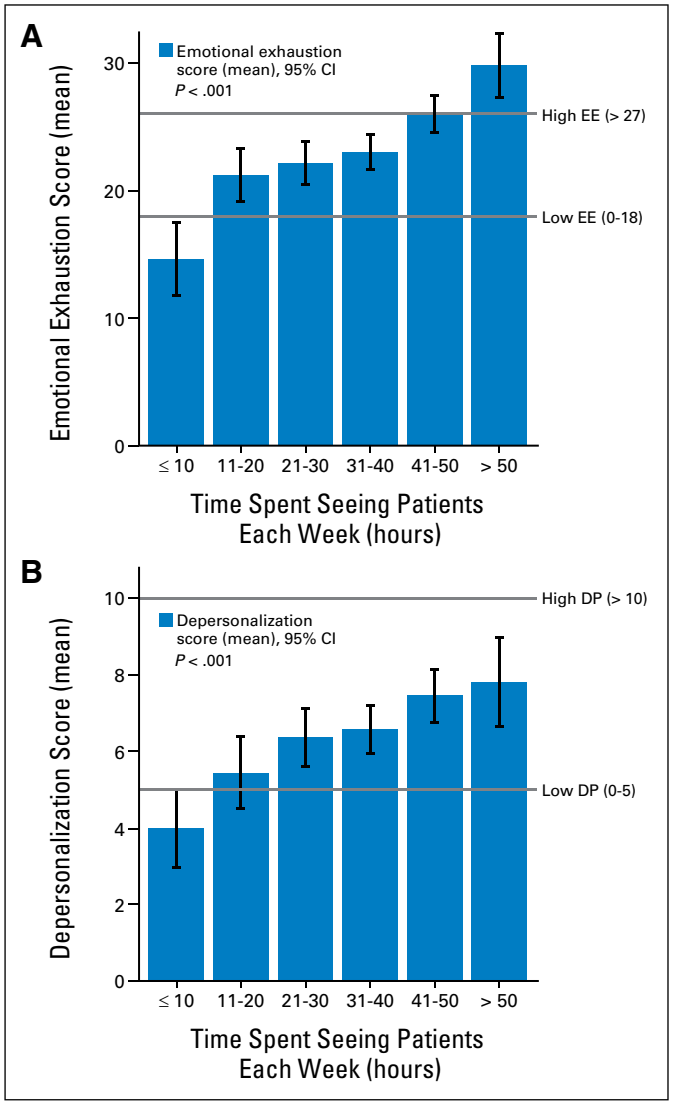

Fig 2. Patient care activity and burnout. The relationship between patient care hours devoted to patient care and burnout among the 985 oncologists who completed the full-length survey and provided information on both hours and burnout is shown. The number of hours spent seeing patients each week is shown on the *x*-axis. Mean burnout score in the (A) emotional exhaustion (EE) and (B) depersonalization (DP) domains is shown in the *y*-axis. Horizontal lines indicate the standardized thresholds to categorize scores for physicians as low, intermediate, or high degree of burnout according to the Maslach Burnout Inventory.

Table 4. Factors Associated With Burnout on Multivariable Analysis

Predictors	OR	95% CI	*P*
All oncologists*†‡			
Age (for each additional year older)	0.961	0.947 to 0.975	< .001
Hours/week spent seeing patients (OR each additional hour)	1.032	1.022 to 1.042	< .001
Hours/week at home spent on work tasks (OR each additional hour)	1.019	1.001 to 1.037	.0392
Focus on one certain type of cancer (*v* multiple focus)	1.422	1.050 to 1.925	.0227
Private practice*†§			
Age (OR each additional year older)	0.953	0.932 to 0.974	< .001
Has children (*v* not)	0.447	0.210 to 0.950	.0363
Hours/week spent seeing patients (OR each additional hour)	1.041	1.020 to 1.063	< .001
Hours/week spent administrative tasks at work/week (OR each additional hour)	1.054	1.018 to 1.092	.0032
Nights on call/week (OR each additional night)	0.877	0.788 to 0.975	.0152
Academic practice*†‖			
Age (OR each additional year older)	0.961	0.935 to 0.987	.0036
Female (*v* male)	1.678	1.020 to 2.762	.0416
Hours/week spent seeing patients (OR each additional hour)	1.023	1.004 to 1.042	.0190
Hours/week spent at home on work tasks (OR each additional hour)	1.035	1.002 to 1.069	.0363
Minutes allotted for a return outpatient appointment (OR each additional minute)	0.964	0.929 to 1.000	.0494
No. of weekends on call/year (for each additional weekend)	1.071	1.015 to 1.130	.0122
Focus on one certain type of cancer (*v* multiple focus)	3.244	1.556 to 6.673	.0017

NOTE. Three multivariable analyses were conducted to identify personal and professional factors associated with burnout. The first model included all oncologists. Given substantial differences in professional characteristics, separate models were also created for PP oncologists and AP oncologists.

Abbreviations: AP, academic practice; OR, odds ratio; PP, private practice.

*Personal characteristics in all models: age, sex, children, youngest child, relationship status, and student loan debt.

†Professional characteristics in all models: hours spent seeing patients/week, hours spent on administrative tasks/week, hours spent working at home performing work tasks/week, No. of nights on call per week, No. of outpatients seen/week, focus on certain type of cancer (yes/no), minutes allocated per new outpatient visit, minutes allocated per return outpatient visit, No. of weekends rounding in hospital/year, and method compensation (salary, salary plus bonus, pure incentive).

‡Additional professional characteristics in all oncologist models: practice setting.

§Additional professional characteristics in PP model: practice setting (single specialty, multispecialty, health maintenance organization).

‖Additional professional characteristics in AP model: percentage of time spent supervising physicians in training.

likely to have children. Oncologists in PP saw nearly twice as many patients each week, were more likely to be compensated in a purely incentive-based model, and were less likely to focus their practice on a specific area of oncology. AP oncologists spent far more time on work tasks when at home and dedicated more of their effort to supervising physicians in training. Although no difference in the overall prevalence of burnout was observed by practice setting on multivariable analysis, many of the risk factors for burnout differed between AP and PP oncologists, suggesting that efforts to reduce burnout will need to be tailored to practice setting.

How does the prevalence of burnout among US oncologists compare with that among US adults and physicians in other specialties? A recent national study exploring the prevalence of physician burnout found that approximately 46% of US physicians were experiencing symptoms of burnout at the time of the study and that the rate of burnout was markedly higher in physicians than in a probability-based sample of US workers.[32] Although a subanalysis from that study suggested oncologists may actually have a lower rate of burnout (prevalence of approximately 38%) than other internal medicine physicians, only 87 medical oncologists were included in that analysis.[1] The prevalence of burnout (approximately 45%) in our sample of more than 1,000 oncologists was similar to that of US physicians overall. It was also consistent with rates observed in other internal medicine subspecialists (approximately 44%) and lower than

rates in general internists (approximately 54%).[32] Notably, satisfaction with career and specialty choice among oncologists in our study (both > 80%) were the highest of any group of physicians we have studied.[26,32,36,37]

How do these findings compare with those of previous studies of oncologists? In 1990, Whippen et al[15] sent a 12-item survey with a single question about burnout to 1,000 oncologists who subscribed to *Journal of Clinical Oncology*. Among the 598 respondents, 56% subjectively reported that they felt burned out. In 2003, Allegra et al[16] administered a similar survey to approximately 7,700 US oncologists. Among the 1,740 (23%) who responded, 61.7% endorsed a yes/no question asking, "Do you feel that you are experiencing any signs of burnout?" These historical studies are difficult to interpret because they did not use standardized metrics to assess burnout. The prevalence of high emotional exhaustion (22% to 53%) and high depersonalization (11% to 30%) as measured by the MBI in studies of oncologists from other countries are consistent with the rates of emotional exhaustion (38.3%) and depersonalization (24.9%) observed in our study.[3,38-41]

Our study is subject to a number of limitations. Although our participation rate of approximately 50% is consistent with[42] or even higher than [26,32,36] physician surveys in general, response bias remains a possibility. We found no statistically significant differences with respect to age, sex, years in practice, or career satisfaction among oncologists who completed the postcard survey, further supporting that responders were representative of US oncologists. It should be noted that several previous cross-sectional studies have failed to identify significant differences between responding and nonresponding physicians.[43] Because our survey was cross-sectional, we were unable to determine causality or the potential direction of effect for the associations observed. A survival bias may account for some associations such as age (ie, unsatisfied people leave the field). Although we were able to compare differences between oncologists in PP and AP, there were too few participants working in other practice settings to make meaningful comparisons.

Our study also has several important strengths. The oncologists in the sample were drawn from the ASCO oncologist registry, a comprehensive list of US oncologists. The survey included oncologists from all career stages and practice types, as well as a large sample of female oncologists. Our mixed-methods survey design (ie, electronic survey, full-length paper survey, postcard survey) led to a high participation rate relative to other national studies of physicians.[16,26,36] The survey collected extensive information on personal and practice characteristics, providing granular insights into relationships among these variables and burnout/career satisfaction.

Given the prevalence of burnout and evidence that it erodes physicians' personal health[6,7,44] and the quality of care they provide,[9-11,45-50] future studies need to focus on how to address this problem. There is currently limited evidence on what interventions reduce the risk of burnout; most available information focuses on individual[17,18,51-53] rather than system approaches.[5,54] The high prevalence of burnout suggests that studies evaluating practice models (team-based care) and structural characteristics in the practice environment that may reduce burnout are needed.

In conclusion, the prevalence of burnout among US oncologists seems similar to or lower than that of physicians in other disciplines. Although approximately 45% of oncologists are experiencing burnout, their career and specialty satisfaction are high. The volume of patient care provided seems to be a dominant contributor to burnout for both AP and PP oncologists; however, a number of other contributing factors seem to differ by practice setting. A better understanding of the factors that sustain career satisfaction and studies testing interventions to reduce oncologist burnout are needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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ORIGINAL REPORT

Randomized Phase III Trial of Temsirolimus and Bevacizumab Versus Interferon Alfa and Bevacizumab in Metastatic Renal Cell Carcinoma: INTORACT Trial

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See accompanying editorial on page 722 and articles on pages 729 and 760

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
To prospectively determine the efficacy of combination therapy with temsirolimus plus bevacizumab versus interferon alfa (IFN) plus bevacizumab in metastatic renal cell carcinoma (mRCC).

Patients and Methods
In a randomized, open-label, multicenter, phase III study, patients with previously untreated predominantly clear-cell mRCC were randomly assigned, stratified by prior nephrectomy and Memorial Sloan-Kettering Cancer Center prognostic group, to receive the combination of either temsirolimus (25 mg intravenously, weekly) or IFN (9 MIU subcutaneously thrice weekly) with bevacizumab (10 mg/kg intravenously, every 2 weeks). The primary end point was independently assessed progression-free survival (PFS).

Results
Median PFS in patients treated with temsirolimus/bevacizumab (n = 400) versus IFN/bevacizumab (n = 391) was 9.1 and 9.3 months, respectively (hazard ratio [HR], 1.1; 95% CI, 0.9 to 1.3; $P = .8$). There were no significant differences in overall survival (25.8 ν 25.5 months; HR, 1.0; $P = .6$) or objective response rate (27.0% ν 27.4%) with temsirolimus/bevacizumab versus IFN/bevacizumab, respectively. Patients receiving temsirolimus/bevacizumab reported significantly higher overall mean scores in the Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI) –15 and FKSI-Disease Related Symptoms subscale compared with IFN/bevacizumab (indicating improvement); however, no differences in global health outcome measures were observed. Treatment-emergent all-causality grade ≥ 3 adverse events more common ($P < .001$) with temsirolimus/bevacizumab were mucosal inflammation, stomatitis, hypophosphatemia, hyperglycemia, and hypercholesterolemia, whereas neutropenia was more common with IFN/bevacizumab. Incidence of pneumonitis with temsirolimus/bevacizumab was 4.8%, mostly grade 1 or 2.

Conclusion
Temsirolimus/bevacizumab combination therapy was not superior to IFN/bevacizumab for first-line treatment in clear-cell mRCC.

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INTRODUCTION

The treatment of advanced renal cell carcinoma (RCC) has been transformed over recent years with introduction of molecularly targeted therapies against vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR).[1-8] Temsirolimus is a highly specific inhibitor of mTOR, the signaling pathway of which is altered in RCC with clear cell histology, of advanced stage, or with poor prognostic features.[9-11] Temsirolimus is an approved treatment for patients with advanced RCC, having demonstrated antitumor activity in a phase II study of predominantly cytokine-pretreated patients with advanced RCC[12] and, in the pivotal phase III trial, improved overall survival (OS) and progression-free survival (PFS) compared with interferon alfa (IFN) as first-line treatment in patients with multiple poor prognostic factors.[2]

Bevacizumab is an antiangiogenic monoclonal antibody against VEGF with activity in RCC.[4,8,13,14] The majority of RCC tumors, most notably in clear-cell RCC arising from inactivation of the von Hippel-Lindau (*VHL*) tumor suppressor gene, are highly vascular and associated with overexpression of VEGF.[13-15] In two large phase III trials, the addition of bevacizumab to IFN for first-line treatment of clear-cell metastatic RCC (mRCC) showed superior efficacy (PFS) compared with IFN alone.[4,8] On the basis of these results, the regimen of IFN in combination with bevacizumab is presently the only combination therapy approved for treatment of RCC.

Both temsirolimus and bevacizumab have single-agent activity in RCC, but the objective response rate (ORR) of each agent alone is modest.[2,16,17] Because these agents target two different mechanisms of RCC pathogenesis, the combination of temsirolimus and bevacizumab has the potential to further improve efficacy and possibly overcome or delay resistance to bevacizumab by concomitantly blocking alternative signaling pathways. In a preclinical study, the combination of temsirolimus and bevacizumab was found to induce tumor regression in nude mice bearing A498 renal tumors on their flanks, whereas neither drug was able to induce tumor regression as monotherapy, suggesting a potentially additive or synergistic effect of the combination treatment (data on file, Wyeth, Collegeville, PA). Safety data obtained from earlier clinical trials of single-agent treatment suggested that temsirolimus and bevacizumab displayed nonoverlapping toxicity profiles.[15,16,18,19] A phase I portion (n = 12) of a phase I/II study in previously treated patients with RCC demonstrated an acceptable safety profile for temsirolimus in combination with bevacizumab at full doses of each agent, with promising activity (seven partial responses).[20] Investigation of Torisel and Avastin Combination Therapy trial (INTORACT), an international, randomized, open-label phase III trial, was undertaken to directly compare combination treatment with temsirolimus/bevacizumab against standard combination therapy of IFN/bevacizumab for first-line treatment of patients with advanced RCC.

PATIENTS AND METHODS

Patients

Key eligibility criteria were histologically or cytologically confirmed advanced (stage IV or recurrent) RCC with a majority component of clear cell histology, no prior systemic treatment for RCC, age ≥ 18 years, Karnofsky performance status ≥ 70%, life expectancy ≥ 12 weeks, at least one measurable lesion per Response Evaluation Criteria for Solid Tumors (RECIST) version 1.0,[21] and adequate organ function. Patients were excluded if they had CNS metastasis, history of major thrombotic or bleeding episode within 6 months, inadequately controlled hypertension (systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 100 mmHg on medication), major surgery or radiation therapy within 4 weeks, or chronic use of antiplatelet agents or corticosteroids. All patients provided written informed consent.

Study Design and Treatments

This randomized, multicenter, phase III trial was conducted at 124 sites in 29 countries. After screening and enrollment, patients were randomly assigned (one to one) to receive either intravenous (IV) temsirolimus (25 mg weekly) plus bevacizumab (10 mg/kg IV every 2 weeks) or IFN (9 million U [MIU] subcutaneously thrice weekly) plus bevacizumab (10 mg/kg IV every 2 weeks). Patients were stratified according to baseline Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic group (favorable, intermediate, or poor)[22] and prior nephrectomy (yes or no). A computerized centrally located randomization system was used to assign patient identification and treatment. Patients received treatment until disease progression, unacceptable toxicity, withdrawal of consent, or death. Toxicity-related dose reductions were allowed for temsirolimus and IFN, but not for bevacizumab. After treatment discontinuation, patients were observed for survival, initiation of subsequent anticancer therapy, and treatment-related serious adverse events (AEs).

The primary end point was independently assessed PFS, defined as time from randomization to either disease progression per RECIST or death by any cause, whichever came first. Secondary end points were investigator-assessed PFS, independently assessed ORR, OS, and safety. Disease-related symptoms and quality of life were assessed as exploratory objectives.

The study was approved by the institutional review board or independent ethics committee of each center and was conducted in accordance with

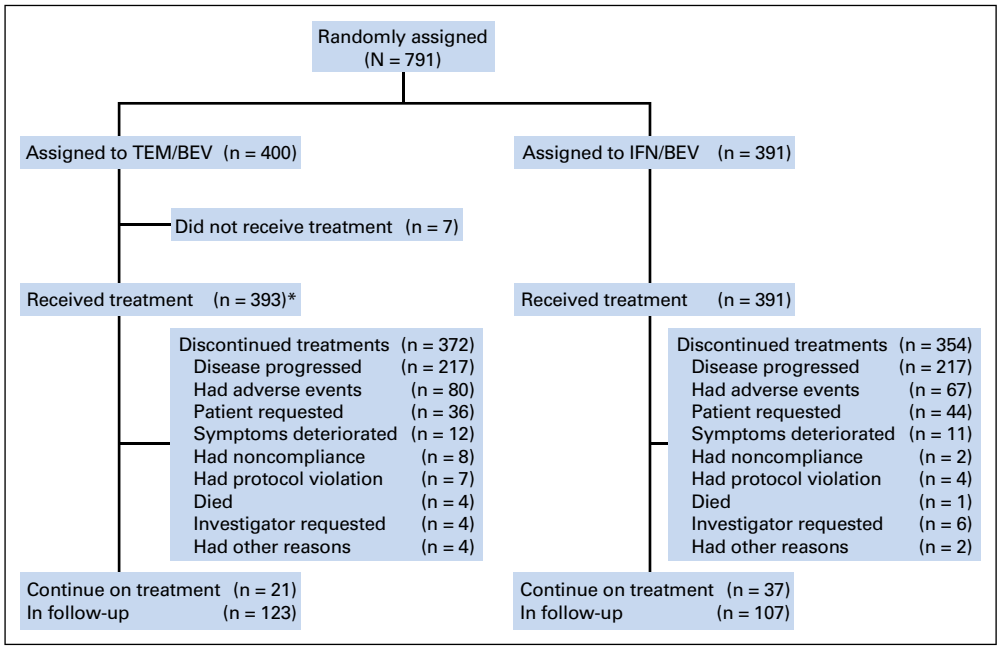

Fig 1. CONSORT diagram of patient disposition. (*) One patient received only one of the allocated treatment drugs (bevacizumab). BEV, bevacizumab; IFN, interferon alfa; TEM, temsirolimus.

the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice, and local regulatory requirements.

Study Assessments

Radiographic evaluations were conducted at screening and every 8 weeks, and tumor progression was assessed both by investigators and by an independent blinded assessment (BioClinica, [formerly Bio-Imaging Technologies], Newtown, PA). Images were read and reviewed by two independent radiologists and, if disagreed, adjudicated by a third reviewer. The reviewers were only given the information on the patient's radiation and surgery history. Bone scan was required at screening and during treatment if signs or symptoms of bone metastases developed. For the primary efficacy end point (PFS), results underwent independent radiographic assessment in accordance with RECIST. Safety and tolerability were assessed throughout the study by physical/clinical examination, hematology and biochemistry tests, and monitoring AEs, which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Health outcomes were assessed at screening, every 8 weeks, and at the end of treatment to explore the patient's own perceptions about his or her quality of life. Assessments were conducted using the Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI) –15, which contains 15 questions representing concerns specific to patients with advanced kidney cancer; FKSI-Disease Related Symptoms (FKSI-DRS) subscale; European Quality of Life-5 Dimensions (EQ-5D), which evaluates five domains (Mobility, Self-Care, Usual Activity, Pain/Discomfort, and Anxiety/Depression); and EQ-5D visual analog scale (EQ-VAS).

Statistical Considerations

The study was originally designed to detect a hazard ratio (HR) of 0.77 (30% improvement in median PFS: 10.2 months for IFN/bevacizumab[4] and 13.3 months for temsirolimus/bevacizumab) with 80% power using a one-sided stratified log-rank test at the 2.5% significance level, with one primary analysis and no interim analysis. A sample size of 800 patients was required for randomization to observe 446 events (death or progression per independent assessment) for the primary analysis, assuming a 15% dropout rate from lost to follow-up and other reasons. Subsequently, one interim analysis based on investigator-assessed PFS was added, before any knowledge of efficacy results, at approximately 236 observed events, and the number of independently assessed events in the final analysis was revised upward to 472. A nonbinding futility boundary, specified by the Pampallona-Tsiatis power spending function (parameter value, 0), and an efficacy boundary, specified by γ (−20) α-spending function, was calculated based on a number of observed PFS events at interim analysis. Because the trial was not to be stopped for efficacy (but for futility only) at interim analysis, testing at the final analysis was done at the nominal 0.025 significance level (one-sided). With 236 observed PFS events, the futility boundary would be crossed if the observed HR was greater than 0.9262.

PFS in the temsirolimus/bevacizumab arm was compared with the IFN/bevacizumab arm using a stratified log-rank test at a 2.5% (one-sided) significance level; HRs and corresponding 95% CIs were generated based on the stratified Cox proportional hazards regression model. The median time to event was estimated using the Kaplan-Meier method. Comparative analysis between the two treatment arms for OS was determined by stratified log-rank

Table 1. Demographic and Baseline Characteristics (intent-to-treat population)

Characteristic	Temsirolimus/ Bevacizumab (n = 400) No.	%	Interferon Alfa/ Bevacizumab (n = 391) No.	%
Age, years				
Median	59		58	
Range	22-87		23-81	
Sex				
Male	286	72	270	69
Female	114	29	121	31
Race				
White	327	82	332	85
Asian	47	12	50	13
Other	2	67	9	2
Karnofsky performance status				
≥ 90%	279	70	288	74
80%	100	25	72	18
70%	20	5	30	8
Unknown	1	< 1	1	< 1
Prior nephrectomy*	338	85	335	86
Prior radiotherapy	44	11	36	9
MSKCC prognostic group (no. of risk factors†)				
Favorable (0)	123	31	114	29
Intermediate (1-2)	230	58	237	61
Poor (≥ 3)	47	12	40	10

Abbreviation: MSKCC, Memorial Sloan-Kettering Cancer Center.
*Per clinical database.
†Includes serum hemoglobin below normal, serum lactate dehydrogenase > 1.5× upper limit of normal, corrected serum calcium > 10 mg/dL, Karnofsky performance status < 80%, and time from diagnosis to randomization < 1 year.[22]

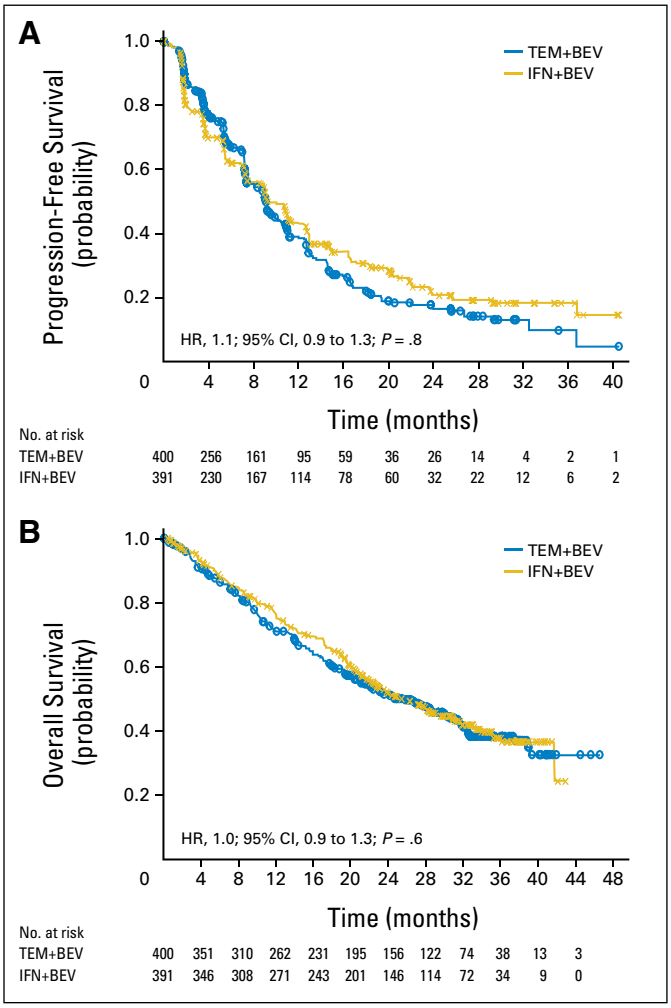

Fig 2. Kaplan-Meier curves of (A) progression-free survival assessed by independent assessment and (B) overall survival assessed by investigators. BEV, bevacizumab; HR, hazard ratio; IFN, interferon alfa; TEM, temsirolimus.

test at the 2.5% (one-sided) significance level. ORRs were compared using the Cochran-Mantel-Haenszel test stratified by prior nephrectomy and baseline MSKCC risk factors, and health outcomes with a repeated-measures mixed-effects model with time as continuous variable and baseline scores as covariate. The minimally important difference was predefined as 3 to 5 points for the FKSI-15[23] and 2 to 3 points for FKSI-DRS[24] to determine a clinically meaningful difference.

East version 5 computer software (Cytel Software Corporation, Cambridge, MA) was used to calculate sample size and stopping boundaries; all other statistical analyses were performed with SAS version 9.1.3 or later (SAS Institute, Cary, NC).

RESULTS

Patients

From April 10, 2008, to October 19, 2010, 791 patients were randomly assigned to receive temsirolimus/bevacizumab (n = 400) or IFN/bevacizumab (n = 391; Fig 1). Seven patients randomly assigned to the temsirolimus/bevacizumab arm did not receive study treatment, and another patient received bevacizumab monotherapy. Baseline demographics and clinical characteristics were well balanced between the two treatment arms (Table 1). Overall, most patients were male (70%), white (83%), younger than 65 years (73%), and had a Karnofsky performance status ≥ 80% (93%), favorable or intermediate MSKCC prognostic group (89%), and prior nephrectomy (85%).

As of the data cutoff date (April 19, 2012), 372 (95%) and 354 (91%) patients in the temsirolimus/bevacizumab and IFN/bevacizumab arm, respectively, discontinued treatment. The main reasons for treatment discontinuation were disease progression (58% *v* 61%, respectively) and AEs (22% *v* 19%, respectively; Fig 1). At the time of data cutoff, in the temsirolimus/bevacizumab and IFN/bevacizumab arm, respectively, 21 and 37 patients remained on treatment, an additional 123 and 107 patients were still alive on study in long-term follow-up, and 210 and 199 patients had died.

Efficacy

The interim futility analysis occurred in June 2010 after 50% of PFS events and the external data monitoring committee recommended the study to continue as planned. For the final analysis, a total of 489 patients (62%) had primary outcome events (427 independently assessed progressions and 62 deaths). On the basis of the final analysis, there was no significant improvement in the primary end point of independently assessed PFS in patients assigned to temsirolimus/bevacizumab compared with IFN/bevacizumab (Fig 2A). Median PFS was 9.1 months (95% CI, 8.1 to 10.2 months) for temsirolimus/bevacizumab and 9.3 months (95% CI, 9.0 to 11.2 months) for IFN/bevacizumab, with an estimated HR of 1.1 (95% CI, 0.9 to 1.3; stratified one-sided $P = .8$). Similar results were obtained for PFS by investigator assessment: median PFS 9.1 months (95% CI, 8.1 to 10.5 months) with temsirolimus/bevacizumab and 10.8 months (95% CI, 9.1 to 11.2 months) with IFN/bevacizumab (HR, 1.1; 95% CI, 1.0 to 1.4; stratified one-sided $P = .9$). PFS results from prespecified subset analyses, including by

Table 2. Independently Assessed Progression-Free Survival by Stratification Factors and Demographic Characteristics (intent-to-treat population)

	Temsirolimus/Bevacizumab (n = 400)				Interferon Alfa/Bevacizumab (n = 391)						
Factor	No.	%	Median PFS* (months)	95% CI	No.	%	Median PFS* (months)	95% CI	HR†	95% CI	*P*‡
Stratification factors at randomization											
Prior nephrectomy											
No	61	15	9.2	7.2 to 11.1	57	15	6.8	2.4 to 7.5	0.8	0.5 to 1.3	.32
Yes	339	85	9.1	8.1 to 10.4	334	85	10.9	9.1 to 12.7	1.1	0.9 to 1.4	.19
MSKCC prognostic group (no. of risk factors)											
Favorable (0)	123	31	11.0	9.0 to 14.5	114	29	11.2	10.7 to 14.9	1.2	0.8 to 1.6	.41
Intermediate (1-2)	230	58	9.2	8.1 to 10.9	237	61	9.1	7.3 to 12.7	1.1	0.9 to 1.4	.42
Poor (≥ 3)	47	12	4.0	3.4 to 7.2	40	10	2.1	1.8 to 5.4	0.8	0.5 to 1.4	.49
Demographic characteristics											
Age, years											
< 65	294	74	9.2	8.1 to 10.5	282	72	9.1	7.4 to 10.9	1.0	0.9 to 1.3	.72
≥ 65	106	27	8.5	7.2 to 12.8	109	28	11.6	7.5 to 16.4	1.3	0.9 to 1.8	.23
Sex											
Male	286	72	9.1	7.6 to 10.2	270	69	10.0	9.0 to 12.7	1.2	0.9 to 1.4	.16
Female	114	29	9.2	7.2 to 12.7	121	31	9.1	6.9 to 12.6	0.9	0.7 to 1.3	.70
Race											
White	327	82	9.0	7.4 to 10.2	332	85	9.3	9.0 to 11.6	1.1	0.9 to 1.3	.49
Asian	47	12	9.2	4.6 to 11.1	50	13	7.1	3.6 to 12.9	1.1	0.7 to 1.7	.77
Region											
EMA region	172	43	9.1	7.4 to 11.1	164	42	12.7	9.3 to 16.5	1.2	0.9 to 1.6	.23
Non-EMA region	216	54	9.2	7.6 to 10.5	210	54	8.6	7.2 to 10.7	1.0	0.8 to 1.3	.92
United States	12	3	5.3	3.7 to NE	17	4	7.5	1.8 to NE	1.5	0.5 to 4.5	.51

Abbreviations: EMA, European Medicines Agency; HR, hazard ratio; MSKCC, Memorial Sloan-Kettering Cancer Center; NE, not estimable; PFS, progression-free survival.

*Median and CI estimates based on quartile estimates produced using the Kaplan-Meier method.

†Compared with interferon alfa/bevacizumab based on an unstratified Cox proportional hazards model.

‡Compared with interferon alfa/bevacizumab based on an unstratified log-rank test.

Table 3. Independently Assessed Best Objective Response by RECIST (intent-to-treat population)

Best Response	Temsirolimus/ Bevacizumab (n = 400) No.	%	Interferon Alfa/Bevacizumab (n = 391) No.	%
Best observed RECIST response				
Complete response	2	< 1	6	1.5
Partial response	106	26.5	101	25.8
Stable disease	218	54.5	184	47.1
Progressive disease	41	10.3	69	17.6
Indeterminate	5	1.3	0	
No postbaseline tumor assessment	17	4.3	18	4.6
Death before first postbaseline assessment	11	2.8	12	3.1
Unknown	0		1	< 1
Overall objective response rate				
Complete + partial response	108	27.0	107	27.4
95% CI	22.7 to 31.6		23.0 to 32.1	
*P**		1.0		

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors.[21]
*Based on a Cochran-Mantel-Haenszel test stratified by prior nephrectomy and Memorial Sloan-Kettering Cancer Center risk groups as randomized (two-sided).

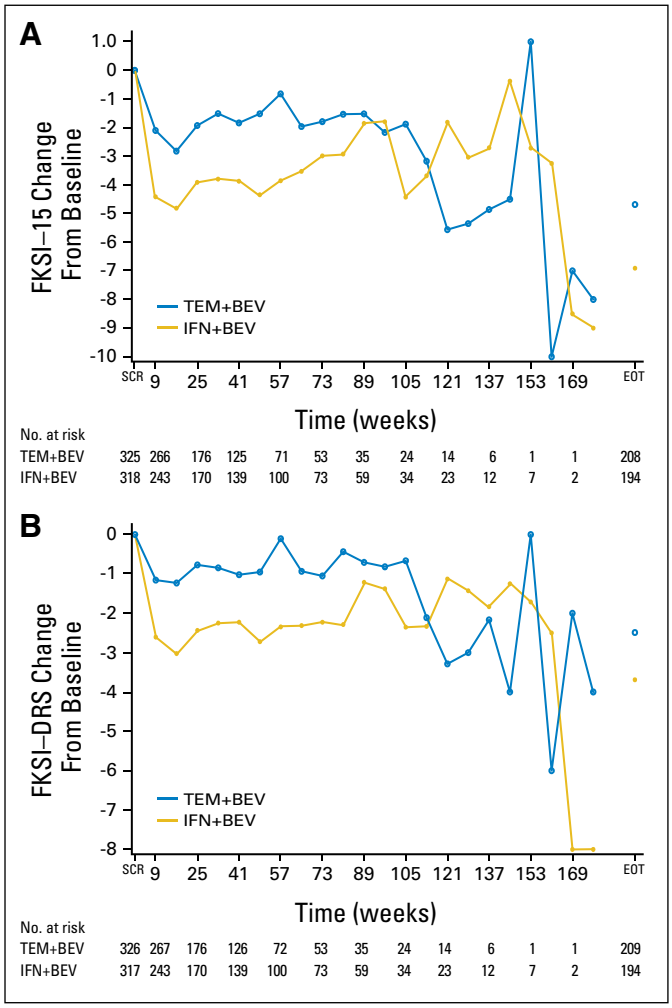

Fig 3. Change from baseline in (A) Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI) –15 and (B) FKSI-Disease Related Symptoms (DRS) scale. BEV, bevacizumab; EOT, end of treatment; IFN, interferon alfa; SCR, screening; TEM, temsirolimus.

stratification factors (Table 2), were consistent with those from the primary analysis; no significant clinical benefit was observed for temsirolimus/bevacizumab in any of the evaluated subgroups (prior nephrectomy, MSKCC prognostic group, age, sex, race, or geographic region).

The independently assessed ORR was 27.0% and 27.4% for temsirolimus/bevacizumab and IFN/bevacizumab, respectively (Table 3), with a risk ratio 1.0 (95% CI, 0.8 to 1.3; $P = 1.0$) adjusted for the baseline stratification factors. Median duration of objective response was 11.3 months (95% CI, 9.0 to 14.8 months) for temsirolimus/bevacizumab and 16.6 months (95% CI, 10.8 to 20.3 months) for IFN/bevacizumab. At the time of data cutoff, OS was not statistically different between the two treatment arms (HR, 1.0; 95% CI, 0.9 to 1.3; stratified one-sided $P = 0.6$; Fig 2B). Median OS was 25.8 months (95% CI, 21.1 to 30.7 months) in the temsirolimus/bevacizumab arm and 25.5 months (95% CI, 22.4 to 30.8 months) in the IFN/bevacizumab arm.

Patient-Reported Outcomes

The completion rate for each questionnaire was uniformly high in both treatment arms, with rates above 90% among patients on treatment up to the end of treatment visit. Analyses were based on observed data without imputation for missing data. Patients in the two treatment arms had almost identical mean scores at baseline. Mean changes from baseline for both FKSI-15 and FKSI-DRS are shown in Figure 3. For both questionnaires, the temsirolimus/bevacizumab arm seemed to maintain a higher (ie, better quality of life) mean score over subsequent cycles. A longitudinal mixed-effects model comparison of the two treatment arms showed that the temsirolimus/bevacizumab arm exhibited significantly higher overall mean scores compared with the IFN/bevacizumab arm for both FKSI-15 (estimated means, 43.3 and 41.5, respectively; $P = .002$) and FKSI-DRS (estimated means, 29.2 and 28.0, respectively; $P < .001$). However, the differences did not meet the predefined minimally important difference threshold (3 to 5 points for FKSI-15 and 2 to 3 points for FKSI-DRS) and hence were considered not clinically meaningful. On the basis of longitudinal mixed-effects model comparison, no statistically significant differences in EQ-5D and EQ-VAS global health outcome questionnaires were observed between the two treatment arms.

Safety and Tolerability

A lower percentage of patients received treatment drugs for more than 48 weeks in the temsirolimus/bevacizumab arm compared with patients in the IFN/bevacizumab arm: 27% versus 33% for temsirolimus versus IFN, respectively, and 26% versus 34% for bevacizumab. Dose reduction owing to AEs in the temsirolimus/bevacizumab arm versus the IFN/bevacizumab arm was 30% *v* 38%, respectively, and treatment delay owing to AEs was 70% *v* 62%, respectively. The most common AE leading to dose reduction was mucosal inflammation (5.1%) in patients treated with temsirolimus/bevacizumab and asthenia (8.4%) in patients treated with IFN/bevacizumab. Dose delays in both arms were mainly due to proteinuria (17% *v* 14%, respectively),

Table 4. Treatment-Emergent Adverse Events of Clinical Interest Reported by ≥ 15% of Patients in Either Treatment Arm

	Temsirolimus/ Bevacizumab (n = 393)				Interferon Alfa/Bevacizumab (n = 391)			
	All Grades		Grade ≥ 3		All Grades		Grade ≥ 3	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Proteinuria	141	36	64	16	106	27	52	13
Hypertension	127	32	44	11	100	26	41	10
Diarrhea	127	32	17	4	87	22	8	2
Hypercholesterolemia	125	32*	23	6*	38	10	5	1
Rash	125	32*	13	3	32	8	3	< 1
Hypertriglyceridemia	114	29	27	7	81	21	16	4
Mucosal inflammation	106	27*	31	8*	39	10	1	< 1
Decreased appetite	104	26	9	2	126	32	13	3
Stomatitis	102	26*	27	7*	38	10	6	2
Asthenia	96	24	23	6	111	28	39	10
Fatigue	92	23	18	5	123	31	42	11
Weight decrease	90	23	7	2	90	23	14	4
Hyperglycemia	86	22*	25	6*	18	5	4	1
Pyrexia	82	21	4	1	153	39†	11	3
Anemia	82	21	36	9	65	17	32	8
Cough	77	20	2	< 1	70	18	1	< 1
Nausea	69	18	3	< 1	76	19	3	< 1
Peripheral edema	66	17*	4	1	30	8	3	< 1
Neutropenia	18	5	7	2	65	17†	32	8†
Myalgia	18	5	0		60	15†	11	3†

*Occurred in a significantly ($P < .001$) higher proportion in the temsirolimus/bevacizumab treatment arm than the interferon alfa/bevacizumab treatment arm.
†Occurred in a significantly ($P < .001$) higher proportion in the interferon alfa/bevacizumab treatment arm than the temsirolimus/bevacizumab treatment arm.

which was one of the most frequently reported treatment-emergent all-grade AEs (Table 4). Other common AEs were diarrhea, rash, hypercholesterolemia, hypertension, hypertriglyceridemia, mucosal inflammation, decreased appetite, and stomatitis with temsirolimus/bevacizumab treatment and pyrexia, fatigue, decreased appetite, asthenia, and hypertension with IFN/bevacizumab. Significantly ($P < .001$) different AEs between the two treatment arms are indicated in Table 4. In addition, the temsirolimus/bevacizumab arm had a higher frequency of renal AEs, infection, and hypersensitivity, but incidence of respiratory, bleeding, and thrombotic AEs was similar between the two treatment arms.

The temsirolimus/bevacizumab arm had a slightly higher incidence of NCI-CTCAE grade ≥ 3 AEs (80% *v* 76%, respectively) and serious AEs (45% *v* 38%, respectively) compared with the IFN/bevacizumab arm. Grade ≥ 3 mucosal inflammation, stomatitis, hypophosphatemia, hyperglycemia, and hypercholesterolemia occurred at a significantly higher incidence with temsirolimus/bevacizumab; grade ≥ 3 neutropenia was statistically higher with IFN/bevacizumab (Table 4). Nineteen patients (4.8%) in the temsirolimus/bevacizumab arm reported pneumonitis, the majority of which was grade 1 or 2.

Of the 409 deaths, 61 occurred during treatment or within 30 days of the last dose: 35 patients (9%) in the temsirolimus/bevacizumab arm and 26 patients (7%) in the IFN/bevacizumab arm. The primary cause of death for the majority of patients was disease progression (42% *v* 44%, temsirolimus/bevacizumab *v* IFN/bevacizumab, respectively). Death resulting from treatment-related AEs was slightly less common in patients treated with temsirolimus/bevacizumab (1%) than with IFN/bevacizumab (1.8%).

DISCUSSION

In this global randomized phase III study, no differences were observed for PFS, OS, or ORR between the combination regimens of temsirolimus/bevacizumab and IFN/bevacizumab when administered as first-line treatment in patients with advanced RCC. No differential PFS benefit between treatment arms was observed when analyzed in predefined subgroups such as prior nephrectomy, MSKCC risk factors, age, sex, race, or geographic region. Similar ORRs were observed in both treatment arms, although the duration of response was numerically shorter with temsirolimus/bevacizumab than with IFN/bevacizumab. Median OS at the time of data cutoff was more than 2 years in both treatment arms. There was improvement in the FKSI-15 and FKSI-DRS scores with temsirolimus/bevacizumab compared with IFN/bevacizumab, although the differences did not meet the predefined clinically meaningful threshold differences, and no global health outcome differences were observed.

AEs observed in this study were consistent with the known safety profiles of temsirolimus, bevacizumab, and IFN. In both treatment arms, frequent grade ≥ 3 AEs were proteinuria and hypertension, both of which are known adverse effects attributable directly or indirectly to the anti-VEGF effects of bevacizumab.[25] In addition, grade ≥ 3 fatigue and asthenia were more common with IFN/bevacizumab treatment. Incidentally, the common AEs observed with IFN/bevacizumab in this study were comparable to those reported in previous phase III trials evaluating the same combination regimen.[4,8] The frequency of some AEs differed between treatment arms in the current study, but were consistent with the unique class-effect toxicities associated with mTOR inhibitors (eg, rash, mucosal inflammation, hypertriglyceridemia, hypercholesterolemia, and hyperglycemia) and IFN (eg, asthenia, fever, anorexia, and chills).[2,19,26] The occurrence of grade ≥ 3 pneumonitis in patients treated with temsirolimus/bevacizumab was 1% in this study, which was similar to that previously reported for temsirolimus alone.[18,27]

This randomized phase III trial was initiated based on the promising, but preliminary, data observed for temsirolimus/bevacizumab in an open-label, phase I/II study,[20,28] which indicated the feasibility of this combination. After the current phase III trial was initiated, results from a randomized phase II trial (TORAVA)[29] in previously untreated patients (n = 171) became available. In TORAVA, the temsirolimus/bevacizumab combination resulted in higher toxicity than anticipated, which limited the duration of treatment; median PFS of 8.2 months and ORR of 27% with temsirolimus/bevacizumab were lower than with IFN/bevacizumab (16.8 months and 43%, respectively). Of note, results from another randomized phase II trial (BEST),[30] evaluating three combinations of targeted therapies (temsirolimus/bevacizumab, temsirolimus/sorafenib, and bevacizumab/sorafenib), indicated that they do not improve PFS over bevacizumab alone in first-line RCC. Combination treatment with temsirolimus and sunitinib, another antiangiogenic agent, in a phase I trial in advanced RCC was terminated because of dose-limiting toxicity at a low dose for each drug,[31] whereas significant toxicities associated with sunitinib in combination with bevacizumab precluded the use of an adequate dosing regimen.[32]

The second approved mTOR inhibitor, everolimus, has also been investigated as combination targeted therapy in advanced RCC. Preliminary reports from an open-label phase II trial of first-line everolimus in combination with bevacizumab have failed to show clinical benefit compared with IFN/bevacizumab (RECORD-2),[33] further confirming lack of evidence that combination therapy simultaneously blocking both VEGF and mTOR pathways offers any advantage over IFN/bevacizumab, other approved single agents, or sequential blocking of VEGF and mTOR pathways.

In conclusion, temsirolimus/bevacizumab was not superior to IFN/bevacizumab as first-line therapy for patients with clear cell mRCC. Safety data were consistent with known profiles of these agents when given as monotherapy. IFN/bevacizumab remains the only combination regimen with demonstrated benefit for first-line treatment of advanced RCC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Manuscript writing: All authors
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GLOSSARY TERMS

Bevacizumab: Also called Avastin, bevacizumab is a recombinant, humanized, monoclonal antibody that binds and neutralizes VEGF, thus acting as an antiangiogenic agent.

IFN-α (interferon alfa): A cytokine with multiple postulated mechanisms that is used as antitumor therapy in several diseases, including metastatic renal cell carcinoma and hairy cell leukemia.

mTOR: The mammalian target of rapamycin belongs to a protein complex (along with raptor and GβL) that is used by cells to sense nutrients in the environment. mTOR is a serine/threonine kinase that is activated by Akt and regulates protein synthesis on the basis of nutrient availability. It was discovered when rapamycin, a drug used in transplantation, was shown to block cell growth presumably by blocking the action of mTOR.

Temsirolimus: Also called CCI-779, temsirolimus is an inhibitor of mTOR, a member of the phophoinositide kinase-related family proteins.

VEGF (vascular endothelial growth factor): VEGF is a cytokine that mediates numerous functions of endothelial cells including proliferation, migration, invasion, survival, and permeability. VEGF is also known as vascular permeability factor. VEGF naturally occurs as a glycoprotein and is critical for angiogenesis. Many tumors overexpress VEGF, which correlates to poor prognosis. VEGF-A, -B, -C, -D, and -E are members of the larger family of VEGF-related proteins.

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SPECIAL ARTICLE

The 41st David A. Karnofsky Memorial Award Lecture: Academic Research Worldwide—Quo Vadis?

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INTRODUCTION

Academia plays a vital role in randomized clinical trials; by counterbalancing commercial interests, it can act as a guardian to protect patients' needs. Moreover, the relationship between investigators and patients enrolling onto clinical trials can be viewed as one based on an implicit ethical contract. Its premise is that the primary objective of randomized clinical trials is to improve patient outcome, free from bias, whether commercial or academic. Indeed, more than 50 years of sustained commitment to randomized clinical trials in early breast cancer have contributed to the declining mortality from the disease in the Western world and would not have been possible without this understanding.[1-3]

The Breast International Group (BIG), created in 1996, is an umbrella organization harnessing the efforts and supporting the activities of its almost 50 national and international cooperative group members worldwide.[4] It has become a major actor in the conduct of early breast cancer trials, particularly those run in partnership with the pharmaceutical industry for the global registration of new anticancer drugs in the adjuvant setting. The HERA (Herceptin Adjuvant) trial (NCT00045032) is one such example, contributing to the registration of adjuvant trastuzumab in 39 countries in fewer than 4 years.[5]

BIG also supports clinical trials sponsored by its academic member groups and facilitates collaboration between international researchers and US cooperative groups. The International Breast Cancer Study Group (IBCSG) –led SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and Exemestane Trial) trials (NCT00066690 and NCT00963417, respectively) evaluating endocrine therapies for 5,738 premenopausal women are cases in point.[6]

BIG is therefore uniquely positioned to examine how academic research in oncology has evolved over the last two decades, to alert the oncology community about the dangerous shift toward commercially oriented research, and to propose some new routes for empowering academics at a critical time when the remarkable progress in elucidating cancer complexity, stemming from The Cancer Genome Atlas (TCGA) project,[7] needs to be translated into new and effective clinical applications.

ACADEMIC EFFORTS TO IMPROVE PATIENT CARE: A CRITICAL LOOK AT THE PAST

The historical evolution of academic research in oncology since the 1960s—in particular in regions outside of the United States—can be roughly divided into three time periods, as illustrated in Figure 1: the golden, silver, and bronze ages. These reflect the progressive weakening of academic leadership, the increasing push by pharmaceutical industries for greater control of clinical trials and data, the implementation of expensive auditable data systems as a result of a few regrettable frauds,[8,9] and the decline in government contributions to an increasingly costly clinical and translational research enterprise. This evolution has distorted the much-needed balance between commercial and public health interests,[10] causing a decline from a formerly golden age to our current, lamentable state of affairs.

It is in this climate that BIG was created; its aims have been to reinvigorate academic involvement in practice-changing trials, to avoid duplication of efforts, and to accelerate the delivery of innovative and efficient therapies to patients with breast cancer. Essential to the process has been a focus on translational research, with its potential to help us understand which patient subgroups could derive the most substantial benefit from often expensive new therapies.[11]

Like other clinical research organizations, BIG built a hybrid model in which academia and industry partner to conduct research oriented toward registering new drugs, while seeking to get national, foundation, or European Commission grants for nondrug- or translation-oriented research. Drug- and nondrug-oriented learning experiences are described in the sections that follow, because they provide insight into the everyday life of academic research organizations today.

Drug-Oriented Research in Partnership With the Pharmaceutical Industry

There are many difficult issues at the academia-industry interface, but successful partnership models do exist, and these can reduce commercial bias as

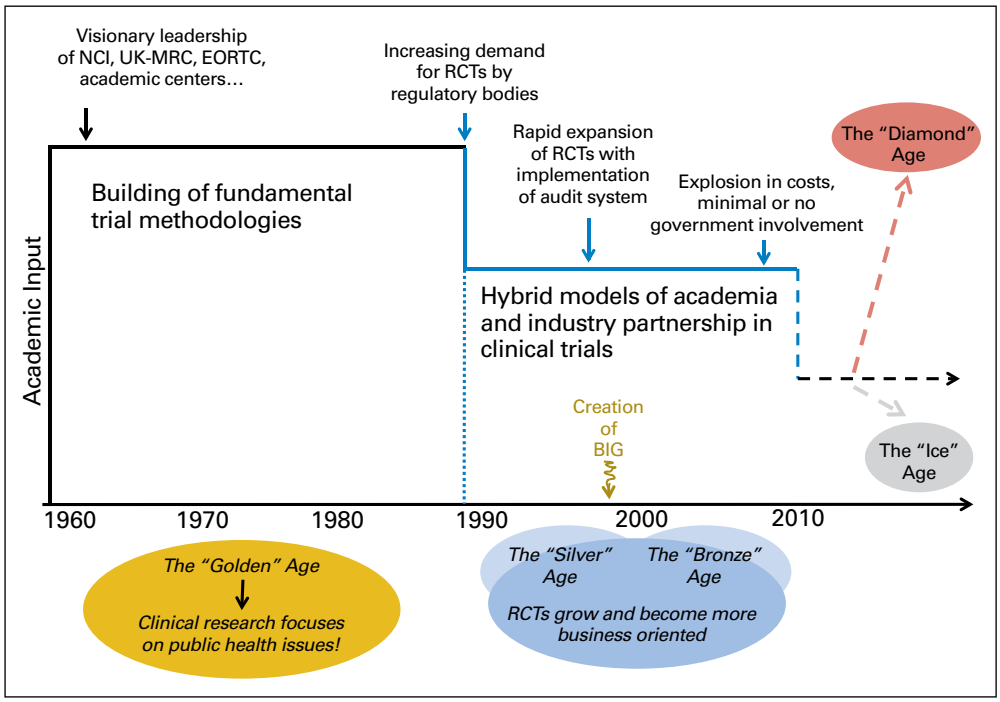

Fig 1. Historical perspective on academic research in oncology. BIG, Breast International Group; EORTC, European Organisation for Research and Treatment of Cancer; NCI, National Cancer Institute; RCT, randomized controlled trial; UK-MRC, United Kingdom Medical Research Council.

well as conflicts of interest between the parties involved, while ensuring the protection of patients.[12,13] Securing such partnerships is therefore essential, but it requires a mutual understanding of the challenges faced by the two worlds.

The pharmaceutical industry is under extreme financial and other pressures. Given increasingly cost-constrained health care systems, limited patent durations on blockbuster drugs, competition from generics, a more demanding regulatory environment, diminished market exclusivity, and progressively smaller markets resulting from the rapidly increasing molecular segmentation of the populations of patients with cancer, companies are being forced to overhaul their drug development strategies.[14]

Academia, in contrast, needs a sense of ownership of the research being conducted as well as preservation of academic freedom; these are essential to preserve the trust patients place in their physicians and to fuel the enthusiasm of investigators, despite a heavily bureaucratic and often discouraging environment.[12,15]

The extensive experience of BIG in close collaboration with industry on pivotal trials in early breast cancer shows that three ingredients are essential to a successful partnership: one, build the partnership on a set of principles; two, devote time to the agenda of each party; and three, respect agreed-on milestones. Successful partnerships in the case of BIG imply rapid cross-continent registration of drugs associated with major clinical benefit, namely, improved disease-free and overall survival without significant risk to patients of either permanent disability or overtreatment.

Until now, most BIG trials have succeeded in meeting the goal of rapid registration of drugs with major clinical benefit. However, the hybrid BIG-industry model has mostly failed to reduce the risk of overtreatment, and as such, it has not always succeeded in serving the best interests of public health care systems nor ultimately of patients.

The IBCSG-led BIG 1-98 trial (NCT00004205) explored in postmenopausal women the value of incorporating an aromatase inhibitor (AI)—letrozole—in the adjuvant treatment scheme for endocrine-responsive breast cancer. The four-arm design of the trial (Fig 2) was the result of an intensive but successful negotiation with the pharmaceutical partner, which, before the involvement of BIG, had started a two-arm comparison of 5 years of letrozole versus 5 years of tamoxifen. Academia finally prevailed by including the sequential treatment options. The outcome of this trial is of great interest to patients, who can experience severe arthralgia and myalgia during AI therapy.[16,17] The trial design that incorporated the academic point of view provided women who experience adverse effects with AIs a viable treatment alternative; BIG 1-98 demonstrated that letrozole followed by tamoxifen for an overall duration of 5 years performed as well as 5 years of letrozole, with the latter shown to be modestly superior to 5 years of tamoxifen.[18]

In contrast to the BIG 1-98 success story, the history of adjuvant clinical trials for human epidermal growth factor receptor 2 (HER2)–positive breast cancer has not been as successful. Although ostensibly revolutionary,[19] trials in this domain reflect a failure on the part of academia to implement an optimal study design. The high cost of HER2-targeted drugs, with a trend toward long treatment durations with multiple add-on drugs, is a striking demonstration of the limited influence of academia and a weakness in the academia-industry partnership overall.

Taking a recent example, BIG, together with US collaborative research groups, has been unable to convince the pharmaceutical industry to move away from the low risk add-on approach in the design of adjuvant registration trials involving the new agent T-DM1. This elegant and truly innovative antibody-drug conjugate uses trastuzumab to transport a potent cytotoxic compound—DM1 or maytansine—to the inside of HER2-positive cancer cells, largely sparing normal tissue.[20] The drug is US Food and Drug Administration (FDA) approved for advanced HER2-positive breast cancer, in view of its superior therapeutic index when compared with the combination of capecitabine and lapatinib in trastuzumab-pretreated patients.[21]

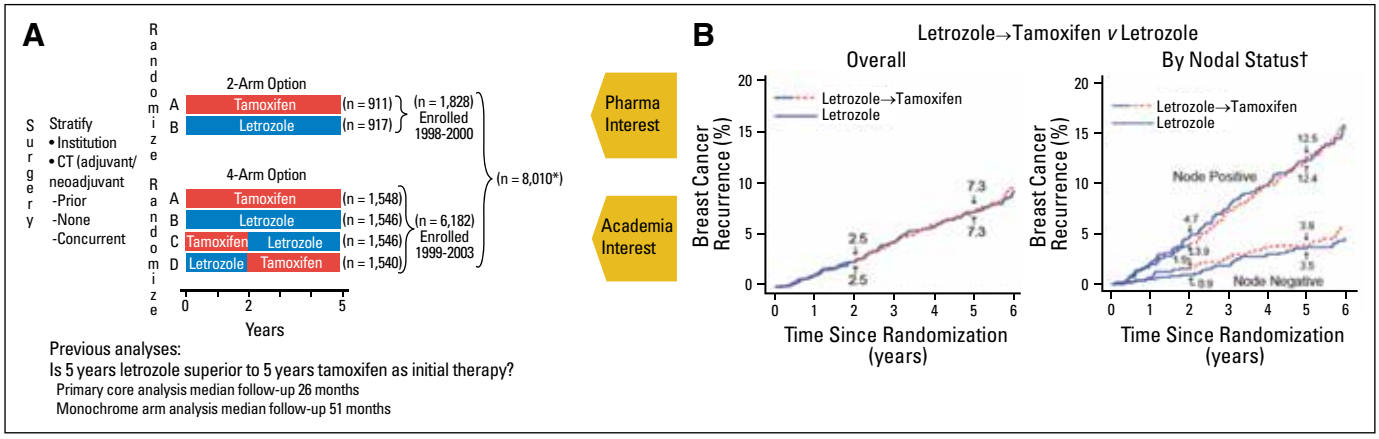

Fig 2. Successes and failures in designing, setting up, and conducting international pivotal clinical trials. The Breast International Group (BIG) experience: moving away from the approach of one strategy fits all. (A) BIG 1-98 overall design. (B) Breast cancer events. (*) Intent to treat (ITT): excludes 18 patients who withdrew consent and did not receive study treatment. (†) 42% of the population is node positive, 58% node negative. CT, chemotherapy.

The current plan of the pharmaceutical industry is to investigate the potential clinical benefit obtained from the addition of T-DM1 to classical treatment using aggressive chemotherapy. Industry cannot be blamed for this preferred route to registration in the current regulatory environment, which places the methodologic bar high, rendering comparisons of efficacy versus toxicity risky. However, this strategy essentially negates the great potential of this drug to show efficacy with reduced toxicity and increased quality of life when used alone in selected women with HER2-positive disease.

Weaknesses in the academia-industry interaction model are also apparent in the earlier conduct of adjuvant registration trials involving trastuzumab, lapatinib, and pertuzumab. Although BIG has been able to conduct three successive, large, global registration trials for early HER2-positive breast cancer with high speed and great efficiency (Fig 3), it has failed to secure patient interests in two ways. First, the optimal duration of anti-HER2 therapy remains largely unknown, meaning that the clinical use of 1 year of trastuzumab in most trials is arbitrarily chosen. Second, the group of patients cured with trastuzumab alone has not yet been identified, implying that the use of an expensive dual HER2 blockade for all patients is a likely scenario, should the results of the ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) and APHINITY (Adjuvant Pertuzumab and Herceptin in Initial Therapy) trials (NCT00490139 and NCT01358877, respectively) be positive.

Unless governments enter into the academia-industry partnership model, little progress is expected in these two areas; the duration of treatment with targeted drugs will continue to be defined according to return on investment calculations with low probabilities of validating shorter therapies in a second generation of noninferiority trials, as is currently happening with adjuvant trastuzumab.[22] Furthermore, biomarker research will continue to suffer from a lack of efficiency in view of the unilateral and often suboptimal funding provided by industry and of fragmentation of efforts as well as sequestration of data to protect ownership on the part of both industry and academia.

Limited sharing of data prevents scientists from seamlessly using the knowledge gleaned from one trial in the development of another, which

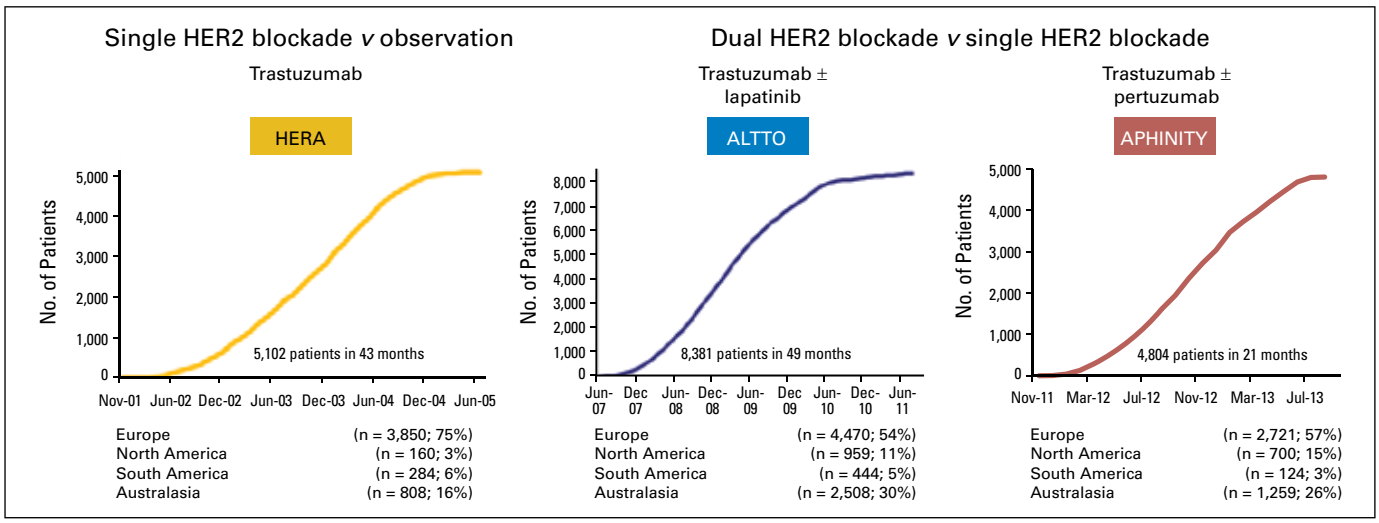

Fig 3. Successes and failures in designing, setting up, and conducting international pivotal clinical trials. The Breast International Group experience: activating trials across continents and recruiting at high speed. ALTTO, Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation; APHINITY, Adjuvant Pertuzumab and Herceptin in Initial Therapy; HER2, human epidermal growth factor receptor 2; HERA, Herceptin Adjuvant.

represents a considerable disservice to patients. The oncology community is poorly prepared to embrace the complexity inherent in the search for predictive biomarkers. Both our limited capability to process large amounts of data generated by high-throughput technologies and the sociology of medical research, with its emphasis on academic career advancement through first-author publications and on the protection of intellectual property, hamper biomarker discovery by encouraging sequestration of data for unacceptably long periods of time.

It has become urgent to put oil into the clinical trial machinery; costs must be reduced through dramatic simplification of bureaucratic procedures,[23] relaxation of monitoring requirements, and participation of governments in covering the cost of standard of care (control arm) treatments administered in the context of clinical trials.

Nondrug-Oriented Research

If drug-oriented research requires strong academic leadership, the need for such leadership is even greater for research focusing on important surgical or radiotherapy questions. Here the search for funding is a veritable crusade, reserved only for the most highly committed investigators prepared to embark on a long journey fraught with obstacles. Two radiotherapy trials conducted under the BIG umbrella have managed to complete accrual thanks to this kind of dedication by their principal investigators. Consequently, the UK Medical Research Council–sponsored SUPREMO (Selective Use of Postoperative Radiotherapy After Mastectomy) trial (NCT00966888) will soon clarify the role, if any, of chest-wall radiotherapy in women with one to three positive nodes who have undergone mastectomy,[24] and a Trans-Tasman Radiation Oncology Group trial (NCT00470236) will help fine-tune the radiotherapy techniques needed to treat ductal carcinoma in situ.

ACADEMIC EFFORTS TO IMPROVE PATIENT CARE: THE FUTURE IS NOW

When academic investigators share the conviction that a particular treatment issue is critical for their patients, when they decide to join forces in an effort to provide a clear answer to the problem at hand, and when they are able to secure funding for the conduct of powerful translational experiments, they greatly empower academic research. This scenario gives us hope that we can transition toward a diamond age. In addition to its patient-centered approach, this scenario embraces the complexity of cancer molecular networks through more ambitious, more open, and more collaborative translational research efforts aimed at better delineating which patients will truly benefit from a particular therapy. Examples of such initiatives exist for several tumor types but are provided here in the field of both early and advanced breast cancer.

Reducing Overtreatment of Early Breast Cancer

Researchers, primarily from academia, have joined forces in recent years in an effort to marry knowledge about early breast cancer biology with new technologies. Their objective is to identify those patients who can be spared aggressive therapies, thereby reducing overtreatment. During the past 15 years, microarray technology has led to the development of several multigene prognostic signatures that are robustly able to identify women with low-stage early breast cancer (defined as $\leq$ three positive axillary nodes) at a very low risk of relapse when untreated with adjuvant chemotherapy.[25] These signatures have little overlap in their respective gene lists, but they share an ability to capture genes involved in proliferation; consequently, their clinical relevance is restricted primarily to luminal breast cancers. These are known to comprise both low and high proliferative subgroups with either favorable or poor clinical outcomes after adjuvant hormonal therapy.[26,27]

It is hoped that two of these gene signatures—Oncotype DX and MammaPrint—will demonstrate, in addition to already proven analytic and clinical validity, their clinical utility above and beyond traditional prognostic variables routinely evaluated by pathologists. The prospective clinical trials TAILORx (Trial Assigning Individualized Options for Treatment) and MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy; NCT00310180 and NCT00433589, respectively), designed to test these signatures, have successfully completed the recruitment of 11,248 and 6,694 patients, respectively, and their results are expected to be reported in 2015.[28,29]

MINDACT, run under the BIG umbrella by the European Organisation for Research and Treatment of Cancer (EORTC), would not have been possible without substantial support from the European Commission, grants from numerous charities, educational grants from three pharmaceutical companies, and the huge commitment of the TRANSBIG consortium, which brought together the expertise of surgeons, medical oncologists, pathologists, laboratory scientists, statisticians, and bioinformaticians. For the results of MINDACT to be positive, the data will have to demonstrate distant metastasis–free survival in excess of 92% at 5 years for the group of women who did not receive adjuvant chemotherapy on the basis of a favorable genomic test despite an unfavorable clinical/pathologic risk assessment according to Adjuvant! Online[30] (Fig 4). With its centralized biobank of frozen and paraffin-embedded tumor samples, serum and blood tumor samples, and—beyond analysis of the 70 genes of prognostic interest—complex genome expression analysis performed on each tumor, MINDACT represents a goldmine for future research in breast cancer, largely under academic control.

Another ambitious international project bringing BIG and US collaborative research groups together under the leadership of SAGE Bionetworks[31] is raising the next wave of enthusiasm in the academic community. By using omics technologies on biobanked material collected in past adjuvant trials, the goal here is to identify patients with early breast cancer with sufficiently good prognosis after conventional therapy who should no longer be enrolled onto trials investigating new and expensive drugs. Such trials would thus be designed for patients with more aggressive disease and higher residual risk for relapse and could be conducted with fewer participants. This initiative would take advantage of large, high-quality data sets split into a public set made available to the broader scientific community and a private set needed for biomarker validation.[32] This project has the potential both to reduce the overtreatment of breast cancer and generate a far more cost-effective way to conduct the adjuvant trials of the future.

Accelerating the Discovery and Validation of Biomarkers Predicting Benefit From Anticancer Drugs

Because adjuvant breast cancer trials take so long and sometimes provide incomplete answers, there has been growing interest in neoadjuvant trials, which allow the in vivo assessment of tumor response, easy access to tissue, and analysis of short-term surrogate end points such as complete pathologic response (pCR). The FDA is seriously

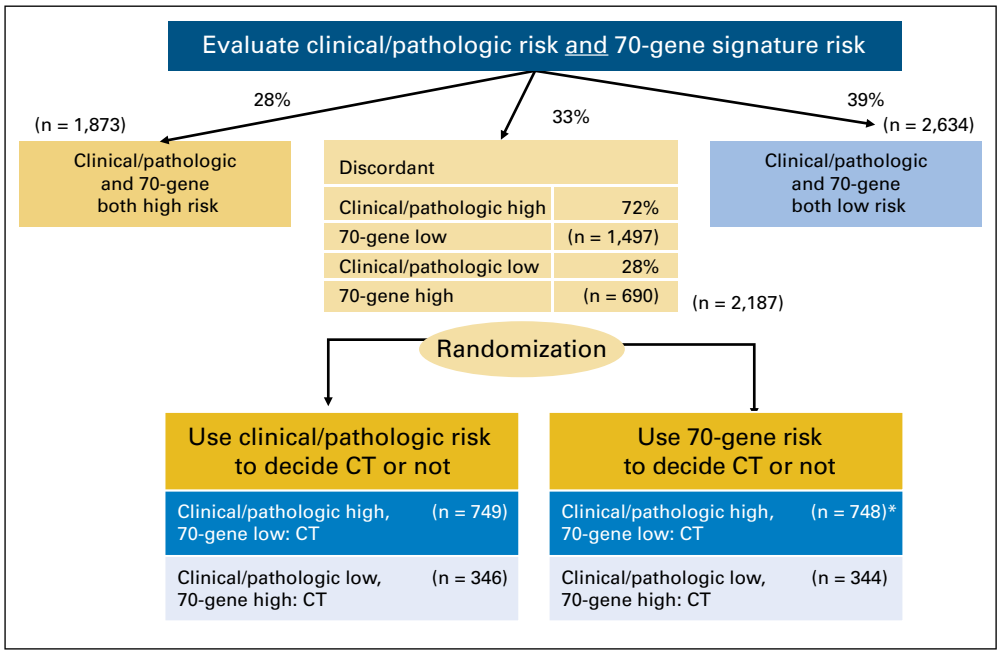

Fig 4. EORTC (European Organisation for Research and Treatment of Cancer) 10041/BIG (Breast International Group) 3-04 MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy) trial design; 6,694 node-negative women and women with one to three positive nodes. CT, chemotherapy. (*) Key subgroup; expected distant metastasis–free survival ≥ 92% at 5 years.

considering an accelerated path to conditional drug approval based on improved pCR rates that later translate into improved disease-free and overall survival.[33] To this end, it coordinated a meta-analysis of neoadjuvant breast cancer trials with mature follow-up that was unable to define the magnitude of pCR gain associated with better disease outcomes, although it nicely underscored the heterogeneity of pCR rates as a function of breast cancer subtype (Cortazar et al, submitted for publication).

The I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis) program in the United States has been built on this vision; it channels new compounds through a neoadjuvant program that combines them with a fixed chemotherapy backbone of sequential anthracycline and taxane. The choice of chemotherapy is justified by preselecting high-risk tumors according to an upfront MammaPrint test.[34] The program identifies the best candidate drugs—namely, those that combine high pCR rates with a putative biomarker of benefit—and upgrades them to the randomized trial, which aims to obtain accelerated, conditional approval. This last step—called I-SPY3—is now ready to be activated, with discussions ongoing with the FDA.

As a network, BIG has taken a different approach to its neoadjuvant research. Namely, for any new drug, it uses knowledge about key molecular pathways for each breast cancer subtype to determine the best likely combination partner from among cytotoxic agents, endocrine agents, or trastuzumab. This is followed by an aggressive, high-throughput, unbiased approach to biomarker discovery using next-generation DNA/RNA sequencing.

When a biologic-window approach is taken, the sequencing is applied first to biopsies taken at baseline and then again at 2 weeks after exposure to the new targeted drugs. The premise is that early drug-induced molecular perturbations might be more predictive of clinical benefit than the baseline biomarker landscape. This approach is complemented by sequential molecular imaging with positron emission tomography–computed tomography undertaken at the same time points at which biopsies are performed. In-depth analysis of any residual tumor at surgery is also planned.

Bringing together a number of international teams with different types of expertise and foreseeing data sharing as soon as possible, the BIG neoadjuvant program (NeoBIG) was launched with the NeoALTTO trial (NCT00553358) for HER2-positive breast cancer. With a second trial about to start and a third in development, NeoBIG has yet to demonstrate its full potential and superior yield, especially compared with the candidate biomarker approach followed in the industry-led NeoSphere trial (NCT00545688).

Both NeoALTTO and NeoSphere, the designs of which are illustrated in Figure 5, have shown an almost doubling of pCR rates with dual HER2 blockade using either trastuzumab and lapatinib (NeoALTTO) or trastuzumab and pertuzumab (NeoSphere) in comparison with single HER2 blockade.[35,36] However, no single baseline biomarker explored in NeoSphere, despite a strong preclinical rationale, has been found to predict for dual HER2 blockade benefit, with the possible exception of programmed cell death protein 1 (PD-1) and signal transducer and activator of transcription 1 (STAT1).[37]

In NeoALTTO, strikingly different metabolic responses have been documented with the biologic therapy, and these responses correlate with pCR. Of particular interest are the data on HER2-positive, hormone receptor–negative tumors that show high probability of pCR (90%) in case of complete metabolic response at 6 weeks (ie, end of biologic window).[38] It will be fascinating to correlate imaging results with biomarker results, and one hopes that this dynamic approach will turn out to be successful in the complex and as yet disappointing search for predictive biomarkers.

The results of the large pivotal trials ALTTO and APHINITY (Fig 3) are expected in 2014 and 2016, respectively, and will allow for robust testing of pCR as a surrogate end point in HER2-positive disease. Moreover, the meticulous tumor- and blood-sample collections in these trials will offer a unique opportunity to validate putative biomarkers generated in the neoadjuvant programs. Of note, these

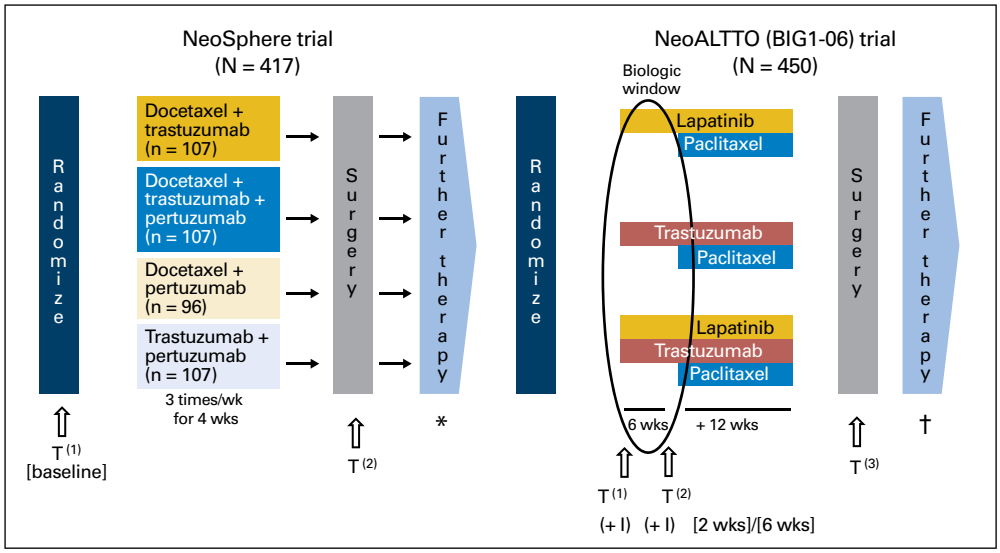

Fig 5. Design of the NeoALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) and NeoSphere trials. BIG, Breast International Group; FEC, fluorouracil, epirubicin, cyclophosphamide; I, positron emission tomography imaging; T, tumor biopsy. (*) Further therapy included FEC × three cycles (first three arms) or docetaxel-FEC (fourth arm) and trastuzumab (to complete 1 year). (†) Further therapy included FEC × three cycles and continuation of same anti–human epidermal growth factor receptor 2 therapy to complete 1 year.

precious biobanks, largely controlled by academia, will be open to the broader scientific community through peer-reviewed processes and for industry-driven research as well. Clearly, the next few years present a test of survival for academic networks with regard to fostering creativity in drug development and delivering clinically useful predictive biomarkers.

Investing Massive Translational Research Efforts in Metastatic Breast Cancer

Progress over the last 30 years has been poor for women with metastatic breast cancer (MBC), as illustrated in a recent publication by Eastern Cooperative Oncology Group (ECOG) investigators.[39] Of 13,785 women enrolled onto 11 ECOG adjuvant trials, 3,447 experienced a distant relapse; their median survival was only 20 months, and this was remarkably stable over time. The only exception was in advanced HER2-positive disease, demonstrating the dramatic impact that improved understanding of disease biology can have on efficient targeted drug development.[40]

Clinical trials for MBC have been largely dominated by the pharmaceutical industry, which tests the activity of its new agents in this palliative setting before embarking on expensive adjuvant registration trials. The academic community has generally neglected MBC, with the exception of interest in circulating tumor cells as potential tools for improved disease monitoring and treatment tailoring.[41] However, there is change on the horizon, with BIG and the North American Breast Cancer Group (NABCG)—as part of their regular meetings to identify unmet medical needs that require global collaboration—recently having decided to join forces in applying next-generation DNA sequencing approaches to study MBC.

To date, DNA sequencing efforts have focused almost exclusively on primary breast tumors, with several recent studies revealing that every tumor has a dominant subclonal lineage, with substantial variation in the number of driver mutations and marked subclonal heterogeneity.[42-46] However, this remarkable research has not yet generated knowledge that can be translated into improved clinical outcomes for patients.

In the meantime, we are already witnessing a dangerous tendency for tumor sequencing to move from the academic world to commercial laboratories. With genomic profile reports now commercially available to physicians and patients alike,[47] we face a significant risk of needing to micromanage advanced breast cancer without any evidence-based knowledge to apply. It is imperative, therefore, that academia take the driver's seat in this exciting but highly complex research area. Rather than embarking on single institutional studies or national programs with a narrow focus, we need broad-scale international initiatives committed to sharing the huge amount of data that will be generated. This is the path that BIG and NABCG have chosen to take together.

The following important questions will be addressed in two large parallel sequencing studies, each involving at least 1,000 patients with MBC and intending to merge their clinical, pathologic, and sequencing data: What are the dynamics of tumor subclonal architecture over time (ie, from primary tumor to metastasis)? What is the relative importance of driver mutations in the so-called trunk of the evolutionary tree and in its branches? How is the genome landscape of the tumor affected by our current drugs? Can truncal and branch driver mutations be captured by tumor DNA in plasma? Which clones are going to play a major role in the lethal evolution of the disease? Answers to these questions could result in truly dramatic changes in the way we treat breast cancer in the years to come.

Figure 6 outlines the BIG sequencing study, which includes the following features: one, both the primary tumor secured in a biobank and one metastatic site will undergo real-time targeted gene sequencing; two, approximately one third of women participating will have actionable mutations, and their participation in downstream trials of new targeted drugs can be proposed; three, all women will be observed longitudinally to gather data on new sites of disease progression and successive therapies; four, patients qualifying as response outliers (defined as rapid progressors or complete responders) will be offered whole-exome and RNA sequencing of both primary and metastatic lesions; and five, plasma will be collected periodically for later analysis of circulating DNA.

Collaboration with the Wellcome Trust Sanger Institute and significant financial support from the Breast Cancer Research Foundation will be key elements to the success of this unprecedented academic research initiative determined to open new avenues of hope for patients with a highly lethal disease.

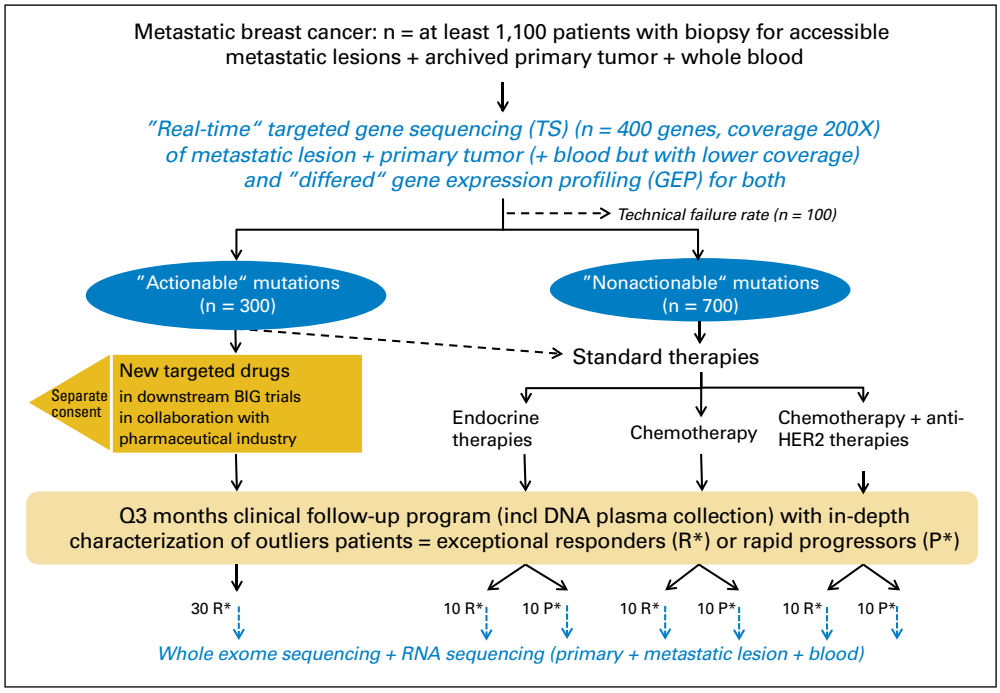

Fig 6. Breast International Group (BIG) academic research program for metastatic breast cancer, 2014-2017. HER2, human epidermal growth factor receptor 2; incl, including.

DISCUSSION

This journey into the history of academic research in oncology based on the experience of BIG has highlighted both the need for and the highly vulnerable nature of partnerships between academic and the pharmaceutical industry, as well as the dangers associated with disinvestment of governments in clinical and translational research. Ensuring academic freedom and early data sharing within these partnerships and enabling more independent academic research are matters of urgency at a critical time for biomedical research. We must now seize the unique opportunity to translate the recent advances in tumor/host genetic profiling into improved treatment tailoring.

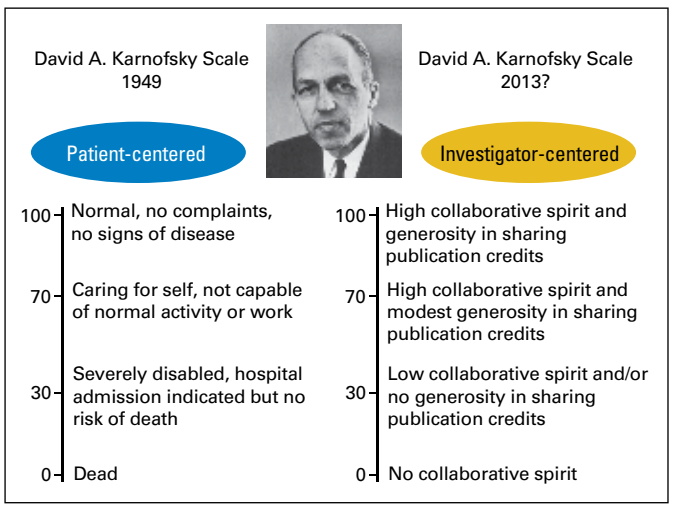

Fig 7. Karnofsky scale.

As team science grows in the 21st century, academic researchers will have to learn how to share investigations, data, and credit. This transition already happened in the world of physics between the 1930s and 1950s[48] and must now take place in cancer research. If David Karnofsky had lived in our exciting times, he would have designed a second Karnofsky scale,[49] centered on the researcher and measuring his or her performance in the research team; on a scale of 0 to 100, 0 would mean the absence of a collaborative spirit, and 100 a high collaborative spirit associated with generosity in sharing data, publications, and credit (Fig 7). The time has also come for universities and scientific journals to join us in embracing this much-needed sociologic revolution.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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SPECIAL ARTICLE

International Myeloma Working Group Consensus Statement for the Management, Treatment, and Supportive Care of Patients With Myeloma Not Eligible for Standard Autologous Stem-Cell Transplantation

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ABSTRACT

Purpose
To provide an update on recent advances in the management of patients with multiple myeloma who are not eligible for autologous stem-cell transplantation.

Methods
A comprehensive review of the literature on diagnostic criteria is provided, and treatment options and management of adverse events are summarized.

Results
Patients with symptomatic disease and organ damage (ie, hypercalcemia, renal failure, anemia, or bone lesions) require immediate treatment. The International Staging System and chromosomal abnormalities identify high- and standard-risk patients. Proteasome inhibitors, immunomodulatory drugs, corticosteroids, and alkylating agents are the most active agents. The presence of concomitant diseases, frailty, or disability should be assessed and, if present, treated with reduced-dose approaches. Bone disease, renal damage, hematologic toxicities, infections, thromboembolism, and peripheral neuropathy are the most frequent disabling events requiring prompt and active supportive care.

Conclusion
These recommendations will help clinicians ensure the most appropriate care for patients with myeloma in everyday clinical practice.

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INTRODUCTION

Multiple myeloma (MM) is a malignant neoplasm that affects primarily elderly patients.[1,2] During the past decade, considerable progress has been made in the management of MM, prompting the International Myeloma Working Group (IMWG) to develop these updated guidelines.[3-6]

METHODS

In 2012, an Update Committee of the IMWG performed a review of key literature, including searches of the Cochrane library, Medline, the Internet, and major meeting reports. Expert consensus was used to propose additional recommendations when published data were insufficient. The Grades of Recommendation, Assessment, Development, and Evaluation system were used to grade recommendations (Appendix Table A1, online only).[7] Some of the treatment regimens recommended for consideration are not approved by the regulatory authorities for these indications and hence should not be considered as standard care but rather as reasonable treatment options. In the recommendations, approved regimens are highlighted in bold font.

RECOMMENDATIONS

Diagnosis

The diagnostic process aims to distinguish between monoclonal gammopathy of undetermined significance, asymptomatic (smoldering) MM, symptomatic MM, solitary plasmacytoma, and other plasma cell diseases based on the IMWG criteria (Table 1). Symptomatic MM is defined as the presence of ≥ 10% clonal bone marrow plasma

Table 1. Diagnostic Criteria for Plasma Cell Diseases

Diagnosis	Diagnostic Criteria
MGUS	All three criteria must be met:
	Serum monoclonal protein (IgG or IgA) < 3 g/100 mL
	Clonal bone marrow plasma cells < 10%
	Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
Smoldering (asymptomatic) MM	Both criteria must be met:
	Serum monoclonal protein (IgG or IgA) ≥ 3 g/100 mL and/or clonal bone marrow plasma cells ≥ 10%
	Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
MM (symptomatic)	All three criteria must be met:
	Clonal bone marrow plasma cells ≥ 10%*
	Presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory MM)
	Evidence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder, specifically:
	Hypercalcemia: serum calcium ≥ 11.5 mg/100 mL
	Renal insufficiency: serum creatinine > 1.73 mmol/L
	Anemia: normochromic, normocytic with hemoglobin value > 2 g/100 mL below lower limit of normal or hemoglobin value < 10 g/100 mL
	Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures
Solitary plasmacytoma	All four criteria must be met:
	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells
	Normal bone marrow with no evidence of clonal plasma cells
	Normal skeletal survey and MRI of spine and pelvis (except for primary solitary lesion)
	Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
Other plasma-cell diseases	Waldenstrom's macroglobulinemia
	Systemic AL amyloidosis
	Monoclonal Ig deposition disease
	POEMS syndrome

Adapted from Kyle Leukemia 2009.
Abbreviations: AL, amyloid light chain; CRAB, hypercalcemia, renal failure, anemia, or bone lesions; Ig, immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MRI, magnetic resonance imaging; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes.
*Monoclonal plasma cells usually account for ≥ 10% of all nucleated cells, but they may range from < 5% to almost 100% (International Myeloma Working Group: Br J Haematol 121:749-757, 2003).

cells and organ damage (hypercalcemia, renal failure, anemia, or bone lesions [CRAB]).[8] In addition, the presence of ≥ 60% bone marrow involvement or rapidly climbing paraprotein, regardless of CRAB, are considered by some authors as MM-related symptoms.[9]

The diagnostic work-up should include three subsequent levels of investigation to confirm the diagnosis, assess the prognosis, and establish the appropriate treatment (Table 2). Serum free-light chain (FLC) assay is useful for diagnosis and monitoring of nonsecretory myeloma, when small amounts of monoclonal protein are secreted in the serum and/or urine, and in light chain–only myeloma.[10-12] Magnetic resonance imaging (MRI) and positron emission tomography integrated with computed tomography (PET/CT) may be useful in selected circumstances (eg, to detect soft tissue lesions arising from bone lesions, spinal cord compression, and asymptomatic lesions and to evaluate a painful area of the skeleton). MRI is indicated in nonsecretory myeloma for initial assessment and follow-up or to detect occult lesions in asymptomatic MM.[13,14]

Recommendations:

- The IMWG criteria should be used to diagnose plasma cell disorders (Grade C/IV; Table 1).
- The recommended investigations of a suspected myeloma should incorporate the tests in Table 2 (grade C/IV).

Pretreatment Considerations: Definitions of Fit and Unfit Patients

The operative cutoff age of 65 years is no longer sufficient to identify elderly patients. Aging is associated with an increased frequency of comorbidities, frailty, and disability, which have a negative effect on outcome.

Age, comorbidities, and geriatric assessment should be used to define patients' status (very fit, fit, and unfit). Unfit patients are characterized by older age, comorbidity, organ dysfunctions (cardiac, pulmonary, hepatic, GI, renal), and limits in mental/mobility functions. To assess comorbidity, the Charlson index can be used.[15] To assess frailty and disability, Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) can be adopted.[16] Fit patients should receive full-dose therapy, whereas unfit patients need reduced dose-intensity treatment.

Recommendation:

- The assessment of organ function, comorbidities (with the Charlson index), frailty, and disability (defined by ADL and IADL) should be considered to define patients' status (grade C/IV).

Staging and Prognostic Factors

The International Staging System (ISS) is used to assess the prognosis of patients with symptomatic MM (Appendix Table A2, online only).[17] ISS stage III is associated with poor prognosis. Chromosomal abnormalities t(4;14), t(14;16), and t(14;20); chromosome 1 abnormalities; and del17p detected by fluorescent in situ hybridization (FISH) are associated with poor prognosis,[18-21] whereas the isolated 13q deletion is not considered a high-risk feature. Hyperdiploidy, t(11;14), and t(6;14) are considered

Table 2. Diagnostic Work-Up for Patients With MM

Work-Up	Description	General Practice	Clinical Trial
First-level investigations to make diagnosis			
History and physical examination		Always	Always
Blood and urine	Complete blood count and differential; chemistry, including creatinine and calcium; serum protein electrophoresis and immunofixation, quantification of immunoglobulin; 24-hour urine collection for proteinuria, electrophoresis, and immunofixation	Always	Always
	Serum free light chains	For oligo and nonsecretory MM and light chain only	Always
Bone marrow	Aspirate and trephine biopsy with plasma cells phenotyping	Always	Always
Imaging	Skeletal survey	Always	Always
Second-level investigations to assess prognosis			
Blood	Albumin, β_2-microglobulin, LDH	Always	Always
	Serum free light chains	Not indicated	Preferred
Cytogenetic	Metaphase karyotype	Preferred	Always
FISH	t(4;14), t(11;14), t(14;16), t(14;20), chromosome 13 deletion, 17p13 deletion, and chromosome 1 abnormalities	Preferred	Always
Third-level investigations required before starting therapy or enrollment onto clinical trials			
Performance status	Karnofsky performance status and WHO scale	Always	Always
Patient status	Assessment of comorbidity, frailty, and disability (cumulative illness rating scale or Charlson score; ADL and IADL score)	Preferred	Always
Organ function	Cardiac, pulmonary, hepatic, GI, and renal function	Always	Always
Infectious disease	Hepatitis B and C, HIV	Always	Always
Additional pretreatment investigations			
Imaging	MRI PET/CT	In selected circumstances	Preferred
Prognostic	GEP	Not indicated	Preferred

Abbreviations: ADL, Activities of Daily Living; FISH, fluorescent in situ hybridization; GEP, gene expression profiling; IADL, Instrumental Activities of Daily Living; LDH, lactate dehydrogenase; MM, multiple myeloma; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography.

standard-risk features. The combination of FISH data with ISS stage improves risk assessment.[20] An abnormal κ/λ FLC ratio at diagnosis seems to predict poor prognosis.[22] Gene expression profiling (GEP) is emerging as a predictive tool to further refine risk stratification.[23,24] The prognostic role of PET/CT has been recently investigated in transplantation-eligible patients,[25] although a standardization of this procedure is needed to translate its use into clinical practice. The achievement of complete response (CR) after initial treatment is associated with improved progression-free (PFS) and overall survival (OS).[26,27]

Recommendations:

- The ISS should always be used at diagnosis (grade C/IV).
- Chromosomal abnormalities should be detected to predict outcome (grade C/IV).
- New prognostic markers (FLC, GEP, and PET/CT) need additional evaluations (grade C/IV).

Indications for Treatment

For asymptomatic patients, close monitoring is suggested every 1 to 3 months. Clinical trials are currently evaluating the role of early therapy with novel agents in high-risk asymptomatic myeloma.[28] Conversely, patients with active and symptomatic MM, defined by the presence of CRAB symptoms, require immediate treatment.

Second-line treatment is indicated when there is either a clinical relapse (reoccurrence of CRAB symptoms) or a significant and quick paraprotein increase (doubled monoclonal protein within 2 months, with an increase in the absolute levels of monoclonal protein of $\geq$ 1g/dL in serum or of $\geq$ 500 mg per 24 hours in urine confirmed by two consecutive measurements).[29] Whether to start treatment in case of biochemical relapse (25% increase in the paraprotein from the lowest response value without CRAB symptoms) is an open issue.

Recommendations:

- Asymptomatic patients should be carefully monitored every 1 to 3 months (grade C/IV).
- Initial therapy is indicated when CRAB symptoms occur (grade C/IV).
- Re-treatment is indicated in case of clinical relapse or if the paraprotein has doubled within 2 months (grade C/IV).

Definition of Response to Therapy

The uniform response criteria were recently revised by the IMWG (Table 3).[29,30] The definitions of immunophenotypic CR, molecular CR, and FLC response were introduced to refine the depth of response. MRI and PET/CT have not been incorporated into the response criteria assessment.[29]

Table 3. Response Criteria

Response	Criteria
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessments are needed
sCR	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flow cytometry; two consecutive assessments of laboratory parameters are needed
Immunophenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with > four colors)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5})
VGPR	Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M component plus urine M component < 100 mg/24 h; in patients for whom only measurable disease is by serum FLC level, > 90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed
PR	≥ 50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥ 90% or to < 200 mg/24 h
	If serum and urine M protein are not measurable, ≥ 50% decrease in difference between involved and uninvolved FLC levels is required in place of M protein criteria
	If serum and urine M protein and serum FLC assay are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥ 30%
	In addition, if present at baseline, ≥ 50% reduction in size of soft tissue plasmacytomas is required
	Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed
MR for relapsed refractory myeloma only	≥ 25% but ≤ 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89%
	In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required
	No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
SD	Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed
PD	Increase of 25% from lowest response value in any of following:
	Serum M component with absolute increase ≥ 0.5 g/dL; serum M component increases ≥ 1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL and/or;
	Urine M component (absolute increase must be ≥ 200 mg/24 h) and/or;
	Only in patients without measurable serum and urine M protein levels: difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL);
	Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%)
	Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas
	Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder
	Two consecutive assessments before new therapy are needed

NOTE. Data adapted.[8,9,30a]

Abbreviations: CR, complete response; FLC, free light chain; M, monoclonal; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Recommendation:

- The updated IMWG criteria (Table 3) should be used to assess response every 30 to 60 days during treatment (grade C/IV).

Front-Line Therapy

Patients age 65 to 75 years are generally considered ineligible for autologous stem-cell transplantation (ASCT). Because biologic age can differ from chronologic age, this strict range may differ by approximately 5 years.

Different therapeutic approaches may be adopted according to age and patient status (Table 4). For patients age 65 to 70 years in excellent clinical condition (very fit), or younger patients with comorbidities, a reduced dose-intensity ASCT with melphalan 100 mg/m^2 (MEL100) can be safely adopted instead of full-dose melphalan 200 mg/m^2 (MEL200). For patients age 65 to 75 years in good clinical condition (fit), full-dose conventional chemotherapy is indicated, whereas for frail patients age > 75 years (unfit), or younger patients with comorbidities, reduced dose-intensity therapy is suggested.

The choice of treatment should take into account patient status (Fig 1), the risk/benefit ratio of each regimen (Table 5), and patient quality of life. Patients with newly diagnosed myeloma should be referred to specialized units to receive appropriate care (Appendix, online only).

Reduced-Intensity Autologous Transplantation

In patients age 65 to 70 years, MEL100 followed by ASCT was superior to standard melphalan-prednisone (MP), improving both event-free survival (28 *v* 16.4 months) and OS (58 *v* 37.2 months),[55] but in patients age 65 to 75 years, MEL100 was inferior to MP-thalidomide (MPT; PFS, 19.4 *v* 27.5 months).[31] In patients age 65 to 75 years, bortezomib-based induction, tandem MEL100, lenalidomide-prednisone consolidation, and lenalidomide maintenance led to a median PFS of approximately 4 years.[56] In selected very fit patients, ASCT remains feasible well beyond the age limit of 65 years. As recommended for patients age < 65 years, bortezomib-based induction and lenalidomide maintenance should be considered for patients undergoing ASCT.[57]

Recommendation:

- Very fit patients age 65 to 75 years, unsuitable for MEL200, may benefit from MEL100 (grade B/IIa).

Table 4. Selected Therapeutic Schemas

Regimen	Schedule	CR (%)	PFS/EFS/TTP	OS
Induction regimens				
MPT	Melphalan: 4 mg/m^2 given orally on days 1-7 every 4 weeks for six cycles[31] or 0.25 mg/kg on days 1-4 every 6 weeks for 12 cycles[32]; prednisone: 40 mg/m^2 given orally on days 1-7 every 4 weeks for six cycles[31] or 2 mg/kg on days 1-4 every 6 weeks for 12 cycles[32]; thalidomide: 100 mg/day given orally continuously until progression or intolerance[31] or 200 mg/day continuously for 12 cycles of 6 weeks[32]	13-16	Median, 20.3 months[33]	Median, 39.3 months[33]
CTDa	Cyclophosphamide: 500 mg/wk for six to nine cycles every 3 weeks; thalidomide: 100 mg/day increased to 200 mg/day for six to nine cycles every 3 weeks; dexamethasone: 20 mg on days 1-4 and 15-18 for six to nine cycles every 3 weeks[34]	13	Median, 13 months	Median, 33 months
VMP	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, and 32 (cycles one to four) and days 1, 8, 22, and 29 (cycles five to nine) every 6 weeks for nine cycles; melphalan: 9 mg/m^2 given orally on days 1-4 every 6 weeks for nine cycles; prednisone: 60 mg/m^2 given orally on days 1-4 every 6 weeks for nine cycles[35]; as alternative, bortezomib: 1.3 mg/m^2 on days 1, 8, 15, and 22 every 6 weeks for nine cycles[36]	24-30	Median, 22-27 months	At 2 years, 85% to 87%
VMPT	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, and 32 (cycles one to four) and days 1, 8, 22, and 29 (cycles five to nine) every 6 weeks for nine cycles; melphalan: 9 mg/m^2 given orally on days 1-4 every 6 weeks for nine cycles; prednisone: 60 mg/m^2 given orally on days 1-4 every 6 weeks for nine cycles; thalidomide: 50 mg/day given orally continuously for nine cycles[36]	38	Median, 33 months	At 3 years, 86%[37]
VTP	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, and 32 (cycle one), every 6 weeks, and 1.3 mg/m^2 on days 1, 8, 15, and 22 every 5 weeks (cycles two to six); thalidomide: 100 mg/day given orally for six cycles; prednisone: 60 mg/m^2 given orally on days 1-4 every 6 weeks for six cycles[38]	28	Median, 31 months*	At 3 years, 70%*
VCD	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, and 11 every 4 weeks for four to 12 cycles; cyclophosphamide: 300 mg/m^2 given orally on days 1, 8, 15, and 22 every 4 weeks for four to 12 cycles; dexamethasone: 40 mg/day given orally on days 1-4, 9-12, and 17-20 every 4 weeks for four to 12 cycles[39]; as alternative, bortezomib: 1.5 mg/m^2 given as bolus intravenous infusion on days 1, 8, 15, and 22[40]	39†	—	—
VRd	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, and 11 every 3 weeks for eight cycles; lenalidomide: 25 mg given orally on days 1-14 every 3 weeks for eight cycles; dexamethasone: 20 mg given orally on days 1, 2, 4, 5, 8, 9, 11, and 12 every 3 weeks for eight cycles[41]	37	At 18 months, 75%‡	At 18 months, 97%‡
Rd	Lenalidomide: 25 mg given orally on days 1-21 every 4 weeks for four cycles§; dexamethasone: 40 mg given orally on days 1, 8, 15, and 22 every 4 weeks for four cycles[42]	4	Median, 25 months	At 2 years, 87%
MPR	Melphalan: 0.18 mg/kg given orally on days 1-4 every 4 weeks for nine cycles; prednisone: 2 mg/kg given orally on days 1-4 every 4 weeks for nine cycles; lenalidomide: 10 mg given orally on days 1-21 every 4 weeks for nine cycles[43]	3	Median, 14 months	Not reached

(continued on following page)

Table 4. Selected Therapeutic Schemas (continued)

Regimen	Schedule	CR (%)	PFS/EFS/TTP	OS
Maintenance regimens				
T‖	Thalidomide: 50 mg given orally, increased to 100 mg if tolerated after 4 weeks, until progression[44]	—	Median, 11 months	Median, 38 months
R	Lenalidomide: 10 mg given orally on days 1-21 every 4 weeks until progression[43]	—	Median, 26 months	—
VT	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion every 2 weeks for 2 years or until progression; thalidomide: 50 mg given orally for 2 years or until progression[36,37]	45	Median, 27 months	Median, not reached
Salvage regimens				
V	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, and 11 every 3 weeks for eight cycles and on days 1, 8, 15, and 22 every 5 weeks for following three cycles[45]	6	Median, 6 months	At 1 year, 80%
V-Peg	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, and 11 every 3 weeks; peg: 30 mg/m^2 on day 4 of each cycle for eight cycles or until progression[46]	4	Median, 9 months	At 15 months, 76%
RD	Lenalidomide: 25 mg given orally on days 1-21; D: 40 mg on days 1-4, 9-12, and 17-20 every 4 weeks for four cycles and on days 1-4 for following cycles until progression[47]	14	Median, 11 months	Median, 29.6 months
Carfilzomib	Carfilzomib: 20 mg/m^2 given as 2-10 minute intravenous infusion on days 1, 2, 8, 9, 15, and 16 every 4 weeks (cycle one) and 27 mg/m^2 on days 1,2, 8, 9, 15, and 16 every 4 weeks for up to 12 cycles[48]	0.4	Median, 3.7 months	Median, 15.6 months

Abbreviations: CR, complete response; CTDa, cyclophosphamide-thalidomide-dexamethasone; D, dexamethasone; EFS, event-free survival; FISH, fluorescent in situ hybridization; MPR, melphalan-prednisone-lenalidomide; MPT, melphalan-prednisone-thalidomide; OS, overall survival; PFS, progression-free survival; R, lenalidomide; Rd, lenalidomide plus low-dose dexamethasone; RD, lenalidomide plus high-dose dexamethasone; TTP, time to progression; V, bortezomib; V-Peg, bortezomib plus pegylated liposomal doxorubicin; VCD, bortezomib, cyclophosphamide, and dexamethasone; VGPR, very good partial response; VMP, bortezomib-melphalan-thalidomide; VMPT, bortezomib-melphalan-prednisone-thalidomide; VTP, bortezomib-thalidomide-prednisone.

*For both patients enrolled in VTP or VMP arms; study detected no significant difference between two treatment arms (VMP *v* VTP).

†Immunofixation-negative CR plus immunofixation-positive CR.

‡With or without transplantation.

‖Patients with adverse interphase FISH receiving thalidomide showed no significant PFS benefit and worse OS ($P = .009$).

§After four cycles, patients could discontinue therapy to pursue stem-cell transplantation or continue treatment until disease progression.

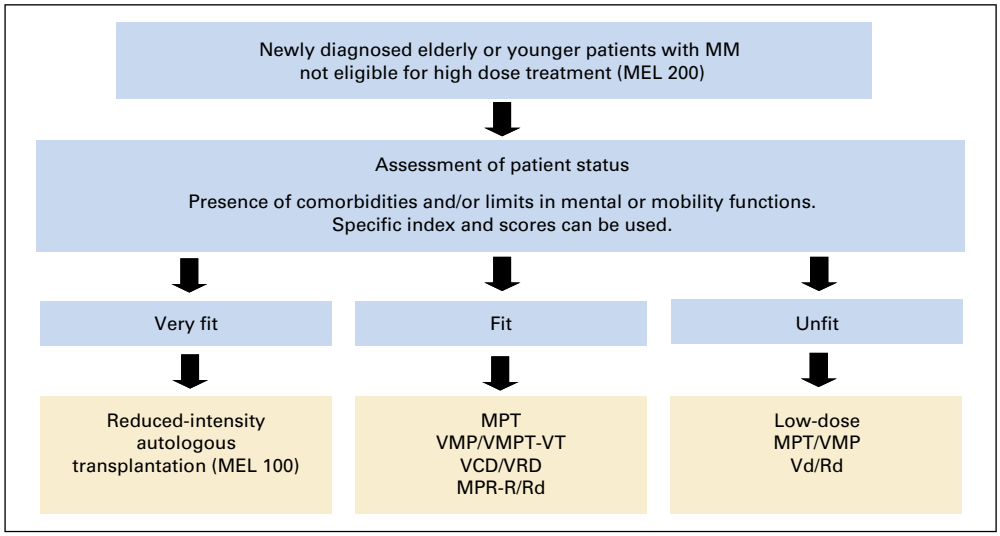

Fig 1. Treatment algorithm for elderly patients with multiple myeloma (MM). MEL 100, melphalan 100 mg/m^2; MEL 200, melphalan 200 mg/m^2; MPR-R, melphalan-prednisone-lenalidomide followed by lenalidomide; MPT, melphalan-prednisone-thalidomide; Rd, lenalidomide plus low-dose dexamethasone; Vd, bortezomib-dexamethasone; VCD, bortezomib-cyclophosphamide-dexamethasone; VMP, bortezomib-melphalanprednisone; VMPT-VT, bortezomibmelphalan-prednisone-thalidomide followed by bortezomib-thalidomide; VRD, bortezomib-lenalidomide-dexamethasone.

Thalidomide-Based Regimens

Thalidomide combined with dexamethasone (TD) was superior to high-dose dexamethasone for partial response (63% *v* 41%)[58] and time to progression (TTP; 22.6 *v* 6.5 months)[59] but was more toxic. Similarly, TD was superior to MP for responses, but PFS was similar, and OS was shorter.[60]

Six randomized studies compared MPT with standard MP. Despite differences in doses and schedules among the trials, better responses and PFS were reported with MPT.[31,32,49-53] The effect on OS varied across the studies, and only two trials showed a significant survival benefit.[31,52] In a meta-analysis of data from 1,682 patients, MPT improved PFS by 5.4 months and OS by 6.6 months.[33] Severe adverse events (AEs), especially nonhematologic, were higher with MPT and negatively affected the prognosis.[53] Thalidomide-related AEs included cytopenia, thrombosis, fatigue, and peripheral neuropathy.

Cyclophosphamide-thalidomide-dexamethasone improved responses compared with MP, with similar survival outcomes and higher incidence of AEs.[34] Thalidomide doses > 100 mg per day are poorly tolerated and not appropriate for elderly patients. MPT has the advantage of oral administration and reduced hematologic toxicity, but it is associated with an increased risk of peripheral neuropathy, deep-vein thrombosis, and cardiac events. The use of this combination is supported by different phase III trials.

Bortezomib-Based Regimens

In a large phase III trial, the addition of bortezomib to standard MP (VMP) significantly increased CR from 4% to 30%, TTP by approximately 7 months, and OS by 13 months.[35,61] Bortezomib-related AEs included primarily neutropenia, thrombocytopenia, and peripheral neuropathy.[62] When the twice-per-week bortezomib

Table 5. Grade 3 to 4 AEs

Regimen	Neutropenia (%)	Thrombocytopenia (%)	VTE (%)	Peripheral Neuropathy (%)*	Infection (%)	Fatigue (%)	GI (%)	SPM (%)
Induction								
MPT[31,32,49-53]	16-48	3-14	3-12	6-23	4-28	3-8	5-11	NA
CTD[34]	NA	NA	16	7	13	NA	4	NA
VMP[35]	40	37	1	22	10	8	17	6
VMP weekly[54]†	33	19	3	8	11	4	6	NA
VMPT[36]	38	22	5	15	13	6	6	NA
VTP[38]	22	12	2	9	1	NA	2	NA
VRd[41]	9	6	5	6	5	3	2	NA
Rd[42]	20	5	12	2	9	9	NA	NA
MPR[43]	66	40	5	0	13	2	5	2
Salvage								
V[45]	14	30	0	8	13	6	19	NA
V-Peg[46]	29	23	1	4	3	6	14	NA
RD[47]	41	15	15	2	22	6	10	NA

Abbreviations: AE, adverse event; CTD, cyclophosphamide-thalidomide-dexamethasone; MPR, melphalan-prednisone-lenalidomide; NA, not available; Rd, lenalidomide plus low-dose dexamethasone; RD, lenalidomide plus high-dose dexamethasone; SPM, second primary malignancy; V, bortezomib; V-Peg, bortezomib plus pegylated liposomal doxorubicin; VMP, bortezomib-melphalan-thalidomide; VMPT, bortezomib-melphalan-prednisone-thalidomide; VTE, venous thromboembolism; VTP, bortezomib-thalidomide-prednisone.
*Sensory neuropathy/motor neuropathy/neuralgia.
†Weekly infusion of bortezomib.

schedule was decreased to once per week, the rate of grade 3 to 4 peripheral neuropathy was significantly reduced from 28% to 8%, without affecting efficacy.[38,54] Recently, subcutaneous bortezomib proved to be as effective as intravenous administration, with a reduced risk of peripheral neuropathy.[63]

The four-drug combination of bortezomib, melphalan, prednisone, and thalidomide followed by continuous bortezomib-thalidomide (VMPT-VT) demonstrated better responses and a PFS prolongation of 8 months compared with VMP, but the efficacy advantage was mainly reported in fit patients 65 to 75 years of age.[36,37] Bortezomib-thalidomide-prednisone (VTP) as induction, followed by VT or bortezomib-prednisone, was not superior to VMP and was associated with more serious AEs and discontinuations.[38]

Promising results were obtained when cyclophosphamide (VCD)[39,40] or lenalidomide (VRD)[41] were combined with bortezomib-dexamethasone (VD), producing high-quality responses. Bortezomib, either intravenously or subcutaneously, induces high and rapid responses. Bortezomib does not increase the risk of thromboembolism and may be used in patients with renal failure, but peripheral neuropathy and thrombocytopenia are the main dose-limiting toxicities. The benefits of VMP and VMPT-VT are supported by phase III trials; alternatively, VCD or VRD can be adopted.

Lenalidomide-Based Regimens

The combination lenalidomide plus low-dose dexamethasone (Rd) was better tolerated than lenalidomide plus high-dose dexamethasone (RD), with a significant survival benefit (2-year OS, 87% *v* 75%). The most common grade ≥ 3 AEs were thrombosis, infections, and fatigue and were more frequent with RD.[42]

Melphalan-prednisone-lenalidomide followed by lenalidomide (MPR-R) significantly prolonged median PFS by 17 months in comparison with fixed-duration melphalan-prednisone-lenalidomide (MPR) and by 18 months compared with MP. However, this advantage was not confirmed in patients age > 75 years. During induction, the most frequent AEs were hematologic. The incidence rates per 100 patient-years of hematologic second primary malignancies (SPMs) were 1.92, 1.30, and 0.40 in the MPR-R, MPR, and MP groups, respectively, whereas solid SPMs were heterogeneous and balanced across arms.[43]

Lenalidomide has the advantage of the oral administration and the lack of neurologic toxicity, although myelosuppression is common, and the prevention of venous thromboembolism is recommended. MPR-R is supported by a phase III trial, whereas the evaluation of Rd compared with melphalan-based regimens is ongoing.

Recommendations:

- Fit patients should receive full-dose therapy. **MPT, VMP**, Rd, VMPT-VT, and MPR-R are reasonable therapeutic options (grade A/Ib).
- **MPT** may be preferred for its oral administration and lower cost (grade C/IV).
- **VMP** and VMPT-VT or VCD and VRD may be preferred in patients who need rapid, profound cytoreduction. Once-per-week subcutaneous bortezomib should be considered because of the lower incidence of AEs (grade C/IV).
- Rd or MPR-R may be preferred when oral administration and the lack of peripheral neuropathy are major considerations (grade C/IV).

Treatment Options for Unfit Patients

Unfit patients are more susceptible to AEs with subsequent treatment discontinuations that significantly affect dose-intensity and efficacy. In these patients, lower dose-intense therapies are suggested. The three-drug combination MPT has consistently showed a PFS improvement that was less pronounced in patients age > 75 years, whereas VMP was superior to MP in patients age > 75 years.[35,52,61] In a randomized study, the outcome was similar between VD, VMP, and VT-dexamethasone, but the discontinuation rate was lower with VD.[64] The combination Rd was equally effective in younger and elderly patients. Therefore, two-drug combinations such as corticosteroid plus lenalidomide, thalidomide, or bortezomib should be considered safe treatment options for unfit patients.[64-67]

Low-dose dexamethasone is mandatory because of the higher toxicity and mortality rates associated with high-dose dexamethasone.[42] Lower doses of dexamethasone (10-20 mg/wk) are better tolerated. Thalidomide at 50 mg per day and lenalidomide at 15 mg per day are the preferred doses in this setting.[52,68] Subcutaneous once-per-week bortezomib 1 mg/m^2 is highly suggested in unfit patients.[38,54,63] Because the risk of AEs is higher at the beginning of treatment, therapy may be started at lower doses and subsequently increased after 2 to 4 months if tolerated or if the disease is not adequately controlled.

Recommendation:

- Unfit patients should receive reduced-dose **MPT or VMP** or two-drug combinations with bortezomib or lenalidomide and low-dose dexamethasone (ie, Vd or Rd; grade C/IV).

Maintenance Therapy

Maintenance treatment has consistently prolonged PFS but has inconsistently improved survival.[44,69] In a recent meta-analysis, continuous thalidomide improved PFS, with a late OS benefit.[44] In another meta-analysis, lenalidomide reduced the risk of progression by 65% in both young and elderly patients.[70]

In the MRC Myeloma IX trial, the longest PFS was reported in patients treated with thalidomide both at induction and after induction; the shortest PFS was seen in the group treated with MP without thalidomide.[44] Continuous thalidomide showed no PFS benefit and worse OS in patients with adverse FISH.

In a prespecified landmark analysis of the MM015 trial, continuous lenalidomide significantly extended PFS from the start of lenalidomide (26 months) as compared with placebo (7 months), regardless of age.[43] Similarly, VT prolonged median PFS by approximately 14 months.[37] Continuous therapy with VT or bortezomib-prednisone led to a median PFS of 30 months versus 24 months, respectively.[71]

Drug-related toxicity associated with continuous thalidomide therapy may limit its long-term administration. Lenalidomide is well tolerated, although it is also associated with a higher risk of SPMs. Continuous treatment with bortezomib has the inconvenience of injection administration and a slight increased risk of peripheral neuropathy.

In the future, the impact of maintenance on response and outcome after progression needs to be clarified. Similarly, the optimal duration of maintenance should be defined (for a fixed duration of 2 years or until progression/intolerance).

Recommendations:

- The routine use of maintenance in transplantation-ineligible patients is not yet validated.

- Thalidomide is an option for standard-risk patients, although its long-term use is limited by the risk of peripheral neuropathy (grade A/Ib).
- Lenalidomide is well tolerated but associated with a higher risk of SPMs (grade A/Ib).
- Bortezomib can be an effective alternative, with lower risk of peripheral neuropathy than thalidomide (grade B/IIa).

Therapy for Relapsed Disease

When treating patients with relapsed myeloma, duration of response to previous therapy is a fundamental factor to consider. Repeating the same treatment is a valuable option for patients with a durable response lasting more than 20 to 24 months after induction at diagnosis and more than 9 to 12 months after therapy at relapse. In the case of short-term remission duration or progression during initial therapy, an alternative regimen is suggested.

Standard treatments include bortezomib or lenalidomide combined with dexamethasone or bortezomib-pegylated liposomal doxorubicin.[45-47,72,73] Rd is highly suggested because it is better tolerated compared with RD.

Re-treatment with bortezomib is a feasible option.[74] Re-exposure to immunomodulatory drugs such as lenalidomide after previous thalidomide seems feasible; however, efficacy and survival may be lower.[75,76]

In case of stable disease without CRAB symptoms, the treatment strategy should not be changed. The asymptomatic status, rather than a response improvement, is the most relevant factor to consider during salvage treatment.[77] In case of biochemical relapse, especially during maintenance therapy, increasing the dose of the current drug and subsequently adding another agent is a sensible strategy.

In a recent survey, poor outcome was reported once patients became refractory to both bortezomib and immunomodulatory drugs.[78] Ongoing trials are exploring novel agents, such as new proteasome inhibitors (carfilzomib combined with lenalidomide-dexamethasone), anti-CS1 monoclonal antibody (elotuzumab plus lenalidomide-dexamethasone or VD), histone-deacetylase inhibitors (panobinostat and vorinostat), and bendamustine. The US Food and Drug Administration recently approved carfilzomib for progressive MM after at least two prior therapies, including bortezomib and immunomodulatory agents, and pomalidomide in patients relapsed/refractory to lenalidomide.[48,79] Thalidomide is preferred for its limited hematologic toxicity; bortezomib is preferred in case of renal failure or previous deep-vein thrombosis; lenalidomide is suggested in case of concomitant peripheral neuropathy. Palliative care is essential when cure is no longer possible (Appendix, online only).

Recommendations:

- Repeating the same treatment should be considered after long-lasting remission (20-24 months); an alternative regimen is suggested for patients with shorter remission duration (9 to 12 months; grade C/IV).
- **VD or bortezomib-pegylated liposomal doxorubicin** and **lenalidomide-dexamethasone** are the treatments of choice (grade A/Ib).

Bone Disease

Bone disease is a highly disabling event that can cause pain, pathologic fractures, spinal cord compression, and hypercalcemia.[80] Pain requires pharmacologic analgesia, together with chemotherapy, bisphosphonates, and local interventions.[81] Radiotherapy may be useful to prevent further osteolysis at the fracture site; percutaneous vertebroplasty and balloon kyphoplasty are suggested in case of painful spinal fractures.

Oral clodronic acid, intravenous pamidronic acid, and zoledronic acid are the available bisphosphonate treatments.[82-84] Zoledronic acid significantly reduced skeletal-related events (SREs) and improved OS compared with sodium clodronate.[85,86] Zoledronic acid was as effective as pamidronate in preventing SREs.[87,88] No difference was observed between monthly pamidronate at 30 or 90 mg.[89] Renal impairment and osteonecrosis of the jaw are infrequent but serious complications of intravenous bisphosphonates.

Recommendations:

- Analgesics should be used to treat uncontrolled pain. Low-dose radiation therapy (8 Gy, single fraction) of limited involved fields should be used in case of pain not responding to therapy. Vertebroplasty and kyphoplasty should be considered for painful vertebral collapse (grade C/IV).
- Amino-containing bisphosphonates are recommended for the prevention and management of SREs, independently of bone disease status at baseline. Renal function should be carefully monitored, drug doses should be reduced, and dental evaluation should be performed before starting therapy (grade A/Ib). There is insufficient evidence to recommend bisphosphonates in asymptomatic MM.

Renal Failure

Renal failure occurs because of FLC-related damage of proximal tubules, along with hypercalcemia, hyperuricaemia, dehydration, infections, and nephrotoxic drugs. The immediate start of an effective MM treatment is the mainstay to recover renal function. High-dose dexamethasone is a rapid intervention to assure a fall in light chain load.[90] Bortezomib can be administered safely, without dose adjustments, and should be preferred in the event of dialysis.[91-95] Limited data are present on the role of thalidomide in this setting.[96,97] Lenalidomide is active,[98,99] but dose reductions are mandatory depending on the creatinine clearance values.[100,101] Doxorubicin and cyclophosphamide do not require dose adjustments. Adjusted doses of bisphosphonates are indicated to correct hypercalcemia. Additional studies of the new large-pore hemodialysis membranes to physically remove light chains are awaited.

Recommendations:

- High-dose dexamethasone (40 mg per day for 4 days) should be started promptly, along with high fluid intake ($\geq$ 3 L per day of saline solution; grade C/IV).
- In case of acute renal failure or for patients requiring dialysis, bortezomib can be safely used without dose modifications (grade C/IV).
- In case of chronic renal impairment, thalidomide and lenalidomide can be administered. Appropriate lenalidomide dose reductions are mandatory: 10 mg per day when creatinine clearance is 30 to 50 mL/min; 15 mg every other day when creatinine clearance is $<$ 30 mL/min; 5 mg per day after dialysis when patient requires dialysis (grade C/IV).

Hematologic Toxicity

Myelosuppression is primarily induced by chemotherapy, but patient characteristics, disease stage, type of current and previous

treatments, and neutrophil count < 1,000 cells/mL at baseline are additional risk factors of severe neutropenia. Granulocyte colony-stimulating factor (G-CSF) should be used to permit patients to stay on treatment longer.[102,103] Anemia can be managed in the short term with transfusions. Erythropoiesis-stimulating agents are indicated during chemotherapy, particularly with renal impairment, when the hemoglobin concentration is < 10 g/dL, and there is no improvement despite response to therapy.[104-106] Thrombocytopenia is common with bortezomib, lenalidomide, and alkylating agents, whereas it rarely occurs with thalidomide.[103]

Recommendations:

- G-CSF is recommended to prevent febrile neutropenia in patients at high risk based on age, medical history, disease characteristics, and the expected myelotoxicity of chemotherapy.
- When grade 3 to 4 neutropenia occurs during chemotherapy, G-CFS should be added. If neutrophil count restores to > 1,000 cells/mL, therapy can be resumed without dose modifications. If neutrophil count remains < 1,000 cells/mL, treatment should be delayed until neutrophils recovery and resumed at reduced doses (grade C/IV).
- Patients with hemoglobin < 10 g/dL during chemotherapy should receive erythropoietin, which should be stopped if an increase of hemoglobin ≥ 1 g/dL after 4 weeks of treatment is not obtained (grade A/Ib). Iron supplementation is recommended if transferrin saturation is inadequate.
- If grade 4 thrombocytopenia occurs, treatment should be withheld; it can be resumed when the event resolves to grade 2 (grade C/IV).

Thromboembolism

Myeloma has a high risk of venous thromboembolism (VTE).[107] Patient-related risk factors include advanced age, history of VTE or inherited thrombophilia, obesity, comorbidities, central venous catheter in situ, immobility, and surgery. Myeloma-related factors include the diagnosis of myeloma itself, disease burden, and hyperviscosity. Treatment-related factors include the use of thalidomide or lenalidomide, particularly when combined with high-dose steroids or doxorubicin or multiagent chemotherapy, and the concomitant use of erythropoietin.[108-110]

The role of low–molecular weight heparin (LMWH) in preventing VTE is well recognized; aspirin (ASA) should be used in selected circumstances, and fixed low-dose warfarin has generally been shown to be ineffective.[111,112] The American College of Chest Physicians guidelines recommend LMWH or low-dose unfractionated heparin in outpatients with tumors and risk factors for VTE, including thalidomide and lenalidomide therapy.[113]

Recommendations:

- Patients with MM should receive appropriate thromboprophylaxis based on risk factors for the first 4 to 6 months of treatment, until disease control is achieved or as long as the risk of thromboembolism remains high (grade C/IV).
- During thalidomide or lenalidomide treatment, ASA should be administered to low-risk patients (with ≤ one risk factor). High-risk patients (with ≥ two risk factors) should receive prophylactic LMWH or dose-adjusted therapeutic warfarin for 4 to 6 months followed by ASA (grade B/IIa)
- The dose of LMWH should be adjusted according to renal function (grade C/IV).
- For patients who develop VTE, treatment should be temporarily interrupted, and they should receive anticoagulation therapy. When stable anticoagulation is achieved, chemotherapy can be restarted (grade C/IV).

Infections

MM can cause impairment of immune function, with consequent increased risk of infections, particularly during active disease, or treatment with high-dose dexamethasone, myelotoxic agents, or multidrug combinations.[114,115] Herpes zoster is a possible complication related to bortezomib administration.[35]

Recommendations:

- For unfit patients with comorbidities and for patients with an increased infection rate, oral antibiotic prophylaxis should be considered for the first 3 months of therapy. Trimethoprim-sulfamethoxazole prophylaxis should be considered at least during the first 2 to 3 months of chemotherapy or steroid administration (grade C/IV)
- Antiviral prophylaxis, such as acyclovir or valacyclovir, is recommended against zoster reactivation during bortezomib treatment and for 30 to 60 days after its discontinuation (grade C/IV).
- Patients with MM should be treated promptly with broad-spectrum antibiotics in case of fever or suspected infections (grade C/IV).

Peripheral Neuropathy

Peripheral neuropathy can be caused by the disease itself or by thalidomide and bortezomib therapy. Because treatment-emergent peripheral neuropathy is related to the duration of drug exposure and is cumulative,[116,117] early reduction or temporary discontinuation of the drug should be adopted.[118,119] Subcutaneous and weekly bortezomib infusions significantly reduced peripheral neuropathy, without considerably affecting outcome.[116] Neuropathic pain is often poorly responsive to standard analgesia, but gabapentin and opioid drugs may improve symptoms.[120-122]

Recommendations:

- Close monitoring of patients receiving bortezomib and thalidomide is highly recommended. Patients should be informed about the risk of peripheral neuropathy and instructed to promptly seek medical advice when symptoms emerge. When grade 1 peripheral neuropathy with pain or grade ≥ 2 occur, treatment should be interrupted until resolution of symptoms and reinitiated at lower doses (grade C/IV).
- Prompt thalidomide dose reductions (from 100 to 50 mg per day) are essential to avoid irreversible damage (grade C/IV).
- Once-per-week bortezomib at a dose of 1.3 mg/m^2 should be reduced to 1.0 mg/m^2 and subsequently to 0.7 mg/m^2 per week (grade C/IV).

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