

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ

DR. LISA NEWMAN: Thanks, Tom, for that excellent and very well-organized discussion. So, yesterday we heard from two surgical oncologists discussing operative issues in neoadjuvant chemotherapy patients -- Dr. Byrd discussed the issues of surgery in patients with locally advanced breast cancer and inflammatory breast cancer treated with neoadjuvant chemotherapy and then surgery. And we heard from Dr. Terry Mamounas talking about the accuracy of sentinel lymph node biopsy in patients that have received neoadjuvant chemotherapy.

This morning we're very happy to hear from Dr. Barbara Pockaj, who is chair of the section of surgical oncology at the Mayo Clinic in Arizona. And Barbara is going to talk to us about primary management of the breast in patients receiving neoadjuvant chemotherapy.

DR. BARBARA POCKAJ: Thank you. And the name is [pronounced] "Putch-kai", just in case -- no one gets it (Laughs). Alright -- the surgical decisions for patients after neoadjuvant chemotherapy include breast conservation therapy, mastectomy, sentinel lymph node biopsy, which we discussed yesterday, and breast reconstruction, which we're going to discuss after this talk. So, today my talk is really going to focus on breast conservation therapy.

We know our goals of preoperative chemotherapy: Increases the rate of breast conservation therapy. We know that 80 to 90 percent of patients will undergo response to preoperative chemotherapy. Therefore, a large percentage who were only mastectomy candidates could now be offered breast conservation therapy. And, of course, we also obtain prognostic information.

PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ

Now what's our preoperative, pre-therapy assessment? I think a surgeon should evaluate the patient, at least. So this a minimum -- prior to chemotherapy and before surgery. We need to thoroughly document the physical exam. And us surgeons sometimes are lazy on this documentation but this documentation is critical -- to look at the clinical tumor size, location of the tumor, lymph node involvement, skin erosion, fixation to the chest wall, and skin inflammation.

I feel that all patients need to undergo a thorough radiographic evaluation prior to chemotherapy and before surgery. I think mammogram is essential. I think supplemental ultrasound and breast MRI should be used liberally. I feel that all suspicious areas should be biopsied prior to the initiation of chemotherapy; and this may require multiple biopsies.

This is especially important for patients contemplating breast conservation therapy. And I think many patients change their minds. So I think we have to be prepared at the time, when we initially see them before chemotherapy, that all this is actually well documented.

I also feel that, as surgeons, we need to look at these images -- and we need to look at the MRI, the mammogram, the ultrasound as much the radiologists.

Now, I think the location of the tumor needs to be marked in some manner prior to the initiation of chemotherapy. I think this, again, is true even in patients who want mastectomy. I've had several patients change their mind. They come in with a large tumor, they're very upset, they're nervous, they say, "Well, just take it off". They get a wonderful response to preoperative chemotherapy and then they change their minds, and you may be stuck at that time.

**PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ**

We use radiologic clips. You can use coils. Some people have actually advocated, outline the extent of tumor on the breast and then photograph the patient. You could also outline the extent of the tumor on a clear sheet with the appropriate breast markings and use that. I know the Europeans have tattooed the skin, usually at four points, to show where that tumor has been. And the other caveat is that those calcifications will not disappear after preoperative chemotherapy. So these can be used as a target.

If the tumor is not marked before chemotherapy, subsequent localization may prove to be difficult. We know if the tumor shrinks away then you're a little bit in a guessing game. And this may compromise local control. It has been shown that if it wasn't marked preoperatively, your localization may be not exactly correct in about 30 percent of cases.

And if the patient desires breast conservation and the tumor was not marked, you have to use the post-chemotherapy imaging. And a recent study just shown at SSO showed that this may work, especially with breast MRI. But many times you're doing a larger volume of resection, maybe a quadrantectomy.

This was a nice review that has yet to have been published that was given to me from the MD Anderson group. And they looked at their patients who had clips or no clips placed prior to preoperative chemotherapy. And what they have shown is those patients who had no clips had an increased local recurrence to those who did indeed have clips placed preoperatively.

Now what about the timing of this surgery? My personal bias is surgery should be performed after pre-determined chemotherapy is completed -- and this includes patients with dramatic responses to chemotherapy -- unless the oncologist feels they do not want

PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ

to give the patients more chemotherapy. Patients really do not like having to undergo more chemotherapy after surgery. And I think this is an important quality-of-life issue.

Now, you know... there's nothing they don't like more. So, I think if you have a pre-determined chemotherapy regimen, I would go ahead and give it to them and then undergo surgery.

Prior to surgery, hematologic ramifications need to be assessed. You need to make sure that blood counts come back. And I think this is the time all the repeat imaging needs to be performed. And I repeat the exact same imaging we did pre-chemotherapy post-operatively.

Now, everybody has seen this slide, but I think this is important to just review. This is our tumor preoperatively, and we could have two types of shrinkage: One, you could have a nice, concentric shrinkage, which is what we hope for -- that makes our lives easier. Or, you can have what I call either the "honeycomb" or "Swiss cheese" shrinkage. And in this case, obviously, breast conservation -- if this patient wasn't a breast conservation therapy candidate pre-chemotherapy, they're probably not going to be post-chemotherapy. And a radiographic evaluation will really help determine which type of shrinkage we have.

Now, selecting patients for breast conservation therapy are really the same as if the patient had not undergone chemotherapy. We need to have the absence of multi-centric cancer. [In] selected cases, multi-focal cancer may be appropriate. Widespread malignant-appearing calcifications. We need to excise the residual tumor with negative margins and acceptable cosmetic result, and patients have to be willing to undergo radiation therapy. And the decision -- the final decision -- for breast conservation therapy is made after the completion of chemotherapy.

**PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ**

The technique for breast conservation therapy is the same as for those patients who do not undergo preoperative chemotherapy, except the key is we need to excise all residual palpable and radiologic abnormalities. This may require multiple guide wires, or at our institution we use radioactive seeds. And I think nowadays we have onco-plastic techniques that may facilitate breast conservation therapy.

In my opinion, there needs to be meticulous assessment of the margins. Specimens should be inked. We do a six-color inking -- it's very artistic. And adequate margins are controversial. They've had a recent consensus conference; nobody agrees on what is the adequate margin status. Most agree it's somewhere between 1 and 10 millimeters. My preference is 2 millimeters. It needs to be more than 2 millimeters; if not, I go back.

Now, what are some indications for... Or, what are some breast conservation therapy outcomes? Recent German group published their results. They had 602 patients. Of those patients who underwent neoadjuvant chemotherapy, they attempted breast conservation therapy in 81 percent. This was successful in 74 percent of patients, and the majority of patients had initial tumor sizes that were pretty large.

If we look at the factors -- the preoperative predictive factors -- of breast conservation therapy [see slide, "BCT Outcomes, GERPARDUO Trial"]: Smaller tumor to start -- less than 4 centimeters. Preoperative nodal size... Pre-chemotherapy nodal size did not make a difference. Ductal histology was much better than lobular. Grade. Estrogen receptor made no difference. Type of chemotherapy did. Clinical response did. Residual tumor size after chemotherapy -- less than 2 centimeters. And I'll bring up this point, because this number seems to come through in multiple studies. And center size. Those centers that had a wide experience with preoperative chemotherapy did better.

**PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ**

Post-operative factors include pathologic complete response, pathologic nodal status being negative, lymphovascular invasion -- if it was not present, it was better -- and then, multi-focality.

So, in their conclusions was, the majority of patients can undergo breast conservation therapy. The factors that were associated with this are pre- and post-chemotherapy tumor size, response, histology -- and we'll look at this again later, but invasive lobular carcinoma, as we have talked about, already has a lower clinical response and may lead to less breast conservation therapy rate -- lymphovascular invasion, pathologic nodal status, multi-focality, and center size.

This is a single-institution study, and I thought this was well done. This comes from MD Anderson, looking at 340 patients who underwent breast conservation therapy. Overall, their local recurrence was only 9 percent, which is quite good. They found an increased risk of local recurrence with clinical N2 or N3 disease -- that is, pre-chemotherapy -- residual tumor greater than 2 centimeters, multi-focal residual tumor pattern, and lymphovascular invasion.

These are just the graphs, and can show you the differences between these groups. And you can see, in each of these, these are statistically significant.

This led to the development of a prognostic index score that was 1 point for each factor present. I thought this was quite simple -- surgeons like this. (Laughs)

So, you got a total of 0-4 points. They'd shown that those patients who had either a prognostic index score of 0,1 -- a very low risk of local recurrence. And those who had a

**PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ**

score of 3-4 had a higher risk of local recurrence, and in these patients, mastectomy should be considered; though the prognostic index score still needs to be validated on larger datasets.

This shows their data again, with a score of 1, 2, and 3. No group here had 4. You can see quite a difference in either breast recurrence or local-regional recurrence.

Now, what was nice they also put this prognostic index score on their mastectomy and breast conservation therapy patients. And what you can see is there was no difference in those patients who underwent mastectomy or breast conservation therapy who had a prognostic index score of 0 or 1. There was a slight trend starting with prognostic index score of 2, but this was not statistically significant. But it was really quite dramatic for those who had a prognostic index score of 3 or 4.

I have to bring up this study. This study is quite quoted often for a reason not to do breast conservation therapy in patients who undergo preoperative chemotherapy. This was from the French group. It's a retrospective review of 257 patients that were treated between 1985 and 1994.

Of course, this is in the early phase of when we were all learning how to do breast conservation therapy. A variety of chemotherapy regimens were used. A variety of radiotherapy regimens were used. Most patients did have T2 tumors. Most were clinically node-negative. And 92 percent had infiltrating ductal carcinoma. They had local failure rate of, 5 and 10 years of 16 percent and 21.5 percent, which is really quite high.

PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ

These were the factors they had found that were -- that showed increased local recurrence. Those were: young age, tumor close margins or positive margins, S-phase being high, and, again, that residual tumor size of greater than 2 centimeters.

But, of note -- the important thing for this was that there were a significant number of patients who had positive or close margins, unknown, so only two-thirds of these patients truly had negative margins. We found that pre-chemotherapy factors did not play a role. And, in this case, the local recurrence negatively impacted on overall survival.

Nomograms are quite popular in the surgical literature, and I think that this group has published three nomograms that are sometimes helpful, especially for counseling patients. Yesterday, we talked about prediction of a complete response. They also have one for prediction of residual tumor less than 3 centimeters, which they felt was a surrogate for the ability to perform breast conservation therapy. And also a prediction for breast conservation therapy after chemo.

And this is just one of the nomograms for breast conservation therapy. They looked at a variety of factors. You get points, and then you can find what your overall probability is. And the concordant index is fairly good, at 0.67. So I think this is a nice tool and you can use that for counseling of your patients.

Well, what about conversion of those patients who originally were only mastectomy candidates and then became breast conservation therapy candidates? Data regarding local recurrence is somewhat conflicting. Some studies do demonstrate an increased rate of local recurrence; others do not. But there is not a wide variety of literature regarding this.

PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ

No talk is complete without some NSABP data. (Laughs) So, I'll go ahead and talk about B-18. This is well known. Overall, there is no difference in local recurrence in those patients who underwent pre-operative or post-operative chemotherapy. There WAS a difference in those patients who had pre-operative chemotherapy and initially were mastectomy-only candidates and converted to breast conservation therapy and those who were initially breast conservation therapy and stayed. And this had a p-value of 0.04.

They also found that this difference may be due to age and tumor size at presentation. These patients had originally worse tumors, so you would expect that they should not do as well.

The only other data, I think, that was interesting to look at this, was EORTC. And they had the same sort of trial that the NSABP did. They only had 199 patients who underwent breast conservation therapy. And what they found is the overall local recurrence rate was 10 percent in both groups. And they combined both the mastectomy and the breast conservation therapy candidates. But they looked at the group for overall survival -- those who were initially mastectomy patients, or initially breast conservation therapy candidates, and those who converted to breast conservation therapy -- and they found a worse survival in this group. And, again, I think that, again, shows us pre-clinical disease was worse.

One single-institution study which was retrospective, from Europe, from Milan -- these patients were all mastectomy-only candidates. Of these, they had preoperative chemotherapy. 63 percent were able to undergo breast conservation therapy. Again, relatively large tumor size to start, and median follow-up is only 41 months. Again, they found in their breast conservation therapy patients a high percentage of pathologic CRs; again, small tumor size after preoperative chemotherapy.

**PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ**

They had 12 percent margins [that] were positive on final pathology and they're not re-excised -- I'm not sure why. Their overall local recurrence rate was seven percent, but only five percent when the margins were negative. And here you can see 13 percent with the margins positive. Local recurrence did not influence overall survival; but, again, this is a short follow-up. And their conclusion was, margin status is most important overall in local control.

Some special considerations are multi-focal or multi-centric disease. There's one study in the literature that really looks at this. And this, again, comes out of MD Anderson; but looked at all their patients, comparing the uni-focal versus multi-focal cases. For those patients who had multi-focal cancer and who underwent breast conservation therapy, these were patients who had tumors that were able to be removed through one lumpectomy only.

And if they looked at the local recurrence rate between the breast conservation therapy group or the mastectomy group, there was no difference in local recurrence between the two groups. The only caveat -- there were only 20 patients in the multi-focal disease group who underwent breast conservation therapy. So, that's small numbers.

What about infiltrating lobular carcinoma? We've touched on this before. We all know that the pathologic CR rate is much lower in patients who have infiltrating lobular than ductal. Based on that, there's, overall, a lower breast conservation therapy rate in those groups who have infiltrating lobular. And, again, I think these are the Swiss-cheese patients -- they kind of shrink in a Swiss-cheese manner.

PRE-OP THERAPY IN BREAST CANCER
29_SESSION 5_2 - POCKAJ

NSABP-B-27 also looked at the infiltrating ductal versus infiltrating lobular data, and I think there's quite interesting data. That even though we don't know the exact rate of how many underwent breast conservation therapy between the ductal versus lobular, but those patients who did undergo breast conservation therapy -- they had a very low local recurrence rate. So, if you can do it, it's really quite successful.

And, again, clinical prediction of pathologic CR was based on: what was their pre-treatment chemotherapy, the clinical nodal status -- negative to start -- and histologic type; again, lobular had a much lower rate.

So, in conclusion, I think surgeons are integral in the multi-disciplinary approach to breast cancer. We need to see the patients at least before preoperative chemotherapy and after. Breast conservation therapy is safe and effective after preoperative chemotherapy and does increase options for women with breast cancer.

Appropriate selection criteria for breast conservation therapy must be employed. And I think a thorough preoperative assessment is critical. Factors that have been consistently associated with successful breast conservation therapy rate -- though these are not absolute criteria, but I think could be used as a guideline -- I see these in multiple studies, is: less than 2 centimeters of residual tumor, absence of lymphovascular invasion, unifocal disease, histology -- being infiltrating ductal -- and negative margins I think is critical. Thank you.