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Discussion

DR. RONALD K. TOMPKINS (Los Angeles, California): Thank you, President Thompson, Secretary Copeland, Members, and Guests. This is an excellent paper with extremely accurate documentation of a very difficult procedure. I cannot imagine going back in for a third hepatic resection, even if I had been there the first two times. I think it would be very difficult.

The authors have included some things in the manuscript that they have not shown among the slides, and I would like to ask them some questions about it.

First of all, it seems that the median interval between the first and second operation and then the second and third operations grows successively shorter. And I wonder if they would comment on what they are accomplishing in the natural history of the disease by this aggressive approach. What is the role in their experience, and their advice, on the proposal that we should delay operation in patients in whom we have just discovered hepatic metastases, to see if other extrahepatic metastases will materialize in a few months?

This has been proposed by some; I think it is a highly controversial proposal, but I would like to know how they have looked at this and what their data might be.

Secondly, I think that the screening of these patients to rule out extrahepatic malignancy is an extremely difficult thing.

And one of the methods that they have used in their paper, in addition to computed axial tomography scanning and arteriography and portography, has been the use of the positron-emission tomography (PET) scan. And I wonder if they would share with us what they think the role is for PET scanning for detecting extrahepatic metastases, and is this approaching the area where we should use it as a single modality?

And, finally, I noted in the manuscript that many of the patients also had concomitant cryosurgery for their lesions. And I think there was one patient who had only cryosurgery in one of the operations, and I wonder if the authors would tell us what is the role of cryosurgery now in the treatment of hepatic metastases, given some very optimistic and enthusiastic reports that are in the literature relating to that as the best modality for treatment, with equal survival rates to resection.

I think this has been a landmark paper. It is not only an excellent documentation of a good series with very little, actually zero, mortality in the secondary operations and the tertiary operations. But it also is a very thorough review of the literature, and I commend the manuscript to all of you.

Thank you for the privilege of discussing this paper.

DR. JOAQUIN S. ALDRETE (Birmingham, Alabama): President Thompson, Secretary Copeland, I first want to thank Dr. Pinson and Dr. Sawyers for inviting me to discuss this paper and for giving me the manuscript a few hours ahead to discuss it.

I think it is an important paper—I agree with Dr. Tompkins—because there are not many series from one institution that can have ten cases of secondary or tertiary hepatic resections for recurrent metastases to the liver from colorectal carcinoma. Most of the series, I think, that were shown by the authors are multi-institutional series with the inherent problems that those have.

So ten cases from the same institution, and I would like to focus my remarks on those ten cases. I think it is a significant number. It is now clear that hepatic resections for colorectal metastases can be done with almost no mortality. The problem that remains to be clarified is do those patients benefit? Well, I think some patients do benefit, and I think that, as Dr. Sawyers concluded, this was a selected group of patients.

My question is would you tell us more specifically what were the criteria of selection in your patients.

I notice that all of the patients had free margin of resection. And I think uniformly that has been perhaps the most important factor in the long-term survival of patients who undergo this procedure for colorectal metastases. The other ones are the size of the tumors and the number of metastases. I think most of your ten cases were solitary metastases.

Dr. Tompkins touched on another area that I think is significant. And that is, when you see a patient with this problem, should you wait a few months, 1 or 2, and then by that try to select the patients whom their tumor is going to have a different biological behavior. I have been a believer of that. In my own practice, I sort of drag my feet for 1 month or 2 and repeat the computed tomography scan and found that approximately half of the patients in that time had more metastases, and they were not suitable for resection. But the other half, the tumor was not changed, and those were the patients that we have been re-

secting and with results similar to those that Drs. Sawyers and Pinson have presented.

I think that these re-resections benefit a few carefully selected patients because they can improve their quality of life and perhaps prolong their survival time. However, one should avoid the risk of operating in all patients with recurrent hepatic metastases, simply because there is nothing else to offer them.

I appreciate the opportunity to discuss this paper. Thank you.

DR. EDWARD M. COPELAND III (Gainesville, Florida): The problem with the efficacy of the treatment of hepatic metastasis is whether or not we are studying the evolution of metastatic disease eventually destined to destroy the patient, regardless of our therapeutic interventions, or whether or not we are evaluating the efficacy of a specific treatment modality with the hope of cure.

In this series of patients so well presented by Dr. Sawyers, most patients had only a wedge resection as the initial procedure, often without ultrasound in the early phases of the study. Many patients had wedge resection as the second procedure. No doubt, in those patients who recur, we are seeing the evolution of the disease, and the operations are of no therapeutic benefit and, I suspect, of no palliative benefit either.

I have no doubt, however, that hepatic resection of colorectal metastasis is curative in some patients. The question is, in which patients? This is the same question for patients who have most solid tumors, and the attempts to answer these questions is a challenge to surgical oncologists.

The point of Dr. Pinson's manuscript is that second resections can be done, should be done under the appropriate circumstances, can be done safely, and is the only hope of curing some patients.

Again, this is a simple recipe followed by surgeons in the treatment of most solid tumors and is the allure of the field of surgical oncology to which several of us have dedicated our careers.

Now who should have a second hepatic resection? Dr. Pinson, can you be more specific? What was the size of the lesions treated by wedge resection? Did the recurrences appear at distant sites within the liver or in the same liver segment? Would a more anatomical resection have initially prevented persistent disease? Possibly a randomized study on a national level comparing wedge resection with anatomical segmental resection is in order.

Tell us more about the indications for freezing hepatic lesions. Are all patients without extrahepatic disease potential candidates?

I can think of an expensive regimen of hepatic artery infusion followed by hepatic arterial ligation to shrink large lesions, followed by resection and multiple freezings. Does that do any good?

The answer to such questions is a challenge to gifted surgeons such as yourself who can perform these complex operations safely.

I have a very close friend who underwent a radical resection for a Dukes' C rectal cancer and a short time later had a lobectomy for metastatic rectal cancer. He recurred and underwent a second major hepatic resection by the same gifted surgeon, now 5 years ago almost to the day. He is currently disease free.

No question that in him the second resection was valuable, and I still have my friend.

I look forward to the results of your continued study of these vexing surgical questions. Thank you very much.

DR. MARSHALL M. URIST (Birmingham, Alabama): There are some patients who recur with resectable tumor after hepatic resection and do not choose to undergo another operation. What was the survival for this population?

DR. C. WRIGHT PINSON (Closing Discussion): Mr. President, Mr. Secretary, Fellows, and Guests, my co-authors join me in thanking the discussants for their interest in our topic.

Dr. Tompkins, the median or mean intervals between the third and the second operation and between the second and the first operation are not shorter. But I do believe the biology of this tumor is a significant component of the outcome. The survival in the patients who have recurrence who do not undergo a second hepatic operation has been noted by some authors in the median range of 3 to 24 months. The problem with that data is that they are clearly not randomized. Clearly, the patients who do not get reoperated on are a different group.

You raised the issue, as did Dr. Aldrete, about delaying on identifying the recurrence, and that is a concept that has been popularized by Blake Cady from Boston. I can find no reason not to delay 3 to 6 months to observe the natural course and see whether a limited number of lesions grow slowly or whether, in fact, multiple lesions blossom out.

You asked about our use of positron-emission tomography (PET) scanning. We presented data last spring at the digestive disease week on our experience with PET scans. We have found in approximately 30 cases now that it is helpful both to evaluate intra- and extrahepatic recurrence. The PET scan lights up wherever recurrent tumor exists.

We find it is particularly helpful in these repeat cases because you can tell the difference between surgical scar *versus* recurrent tumor. The scan lights up for recurrent tumor, and it is cold for scar.

We find that the important point is the specificity of the PET scan is better than the other modalities. The sensitivity of computed tomography (CT) is pretty good. Sensitivity of CT portography is extremely good. But the difference between PET scan and those other modalities is the specificity of the PET scan is much better than the others and very helpful, again, in these recurrent cases. The final point I would make about PET scanning is that it changed our management in 25% of these patients.

Your next question was about the use of cryosurgery. In 18 of the first 95 patients, cryosurgery was used. In four of the ten patients who had the second hepatic operation, cryosurgery was used.

You asked about the indications for that. We have used it first to assist a standard resection when gross margins were close by freezing that close margin. Second, in conjunction with resection, by using resection on some of the lesions and freezing the deeper and perhaps smaller lesions. Third, we have cryobladed lesions when we have placed an hepatic

artery catheter to increase the overall response to the regional chemotherapy. I would mention that we do not use cryosurgical ablation when we feel that standard resection can be satisfactorily carried out.

We generally only use cryosurgery for very advanced cases. The advantage of cryosurgery is that it makes some lesions easier to handle. And, certainly, by definition, it does increase response to the regional chemotherapeutic regimens. The disadvantages are the coagulopathy and occasional hemorrhage that occurs. The coagulopathy can be quite marked in some patients, with a rise in the prothrombin time, decreased platelets, increased fibrin split products, and a rise in the D. dimer.

The second problem with the cryosurgery is a question about whether you get adequate ablation around large vessels. We have addressed that by either using the Pringle maneuver or total hepatic vascular isolation at the time of the cryoablation. And certainly on the intraoperative ultrasound, it looks like the cryoablation is complete.

In looking at the survival curve and the disease-free survival curves, we can see no difference in those patients who have been cryobladed *versus* those who have had standard surgical resection. But, Dr. Tompkins, I am willing to admit that those are inadequately sensitive methods to answer your question ultimately about whether cryosurgical ablation is effective.

There are two studies that I can think of, though, that looked at the resected specimens of liver after cryoablation. And in those two series, if my recollection serves me well, 7% in one series and 16% in the other had tumor present in the cryoabladed zone.

The last point that I would make about cryoablation is that I think the ultrasound guidance is very crude, and I sometimes worry a great deal about whether we get satisfactory margins because once you start the freeze process, it is very difficult to observe from three dimensions and really tell whether you are getting around that lesion satisfactorily.

Dr. Aldrete, you asked us about our selection criteria. I would say that the principles that apply to second-time resections are the same as those used to select the first-time candidate. In other words, all known disease must be resectable, adequate tissue margins must be obtainable, adequate liver function to tolerate the operation must exist, and no medical disease that would preclude an operation must exist.

There are two key factors to outcome—extrahepatic disease and the ability to obtain a 1-cm margin. Some authors also believe that the number of metastases should be limited. I would tell you that based on the recurrence of our two patients that we went after that had more than three lesions, we would agree with that point.

It is interesting to note that in all of the collective series on repeat resections in the literature at this point in time, there are no other prognosticating factors that are identified other than ability to remove all disease and the ability to gain a 1-cm margin.

Dr. Copeland, I think I have addressed the issue of indications.

I think the issue of what type of resection, a wedge resection or a greater resection, has been answered in the literature reviewing first-time resections. And that is if a 1-cm margin around the tumor has been obtained, it does not matter what

kind of resection is done. And I suspect that that is true of second-time resections as well.

I think I have addressed your issues about freezing.

Dr. Urist, your question is excellent about why did we not resect some of our patients who had recurrence within the liver. We found, as Dr. Sawyers said, approximately a third of our patients had isolated recurrence within the liver. And of those, only 19% were resected. And in the literature, of the isolated recurrence in the liver, the authors report anywhere from 10%

to 40% of those patients. So a minority of patients are selected for repeat resections.

I am unable to give you definitive reasons for why they were not chosen, other than the indications that we discussed earlier. And that may be that we felt that we were going to be unable to gain a 1-cm margin, or we felt that the overall medical condition was such that a repeat operation was unwarranted.

I wish to thank the Association for the privilege of closing this paper and for their interest in our work.