Notes on the potential for metastasectomy in RCC.

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Role of Metastasectomy in MRCC

In 1999 Morton (ref) proposed that " ... a number of series show long-term survival following resection of multiple distant metastases for all histologic types of solid neoplasms. This suggests that it is time to reposition surgery in the treatment paradigm for metastatic cancer." The principal focus of the analysis given by Morton was on metastatic melanoma. In this paper we have begun the process of gathering together published data to stimulate a similar analysis for metastatic RCC (MRCC).

Our background is scientific and not clinical, and we apologize in advance for those parts of this effort which would have been filtered out by someone with clinical experience. However, if we did have a clinical background, we almost certainly would not have had time to collect this data together!

We have done our best to find the most relevant papers within the limits of the time available. We would like to extend this collation with suggestions from the board, or elsewhere. We were probably reasonably effective at finding many of the relevant surgical papers, as their title tends to be specific. However we are certain that we have missed some useful immunotherapy papers - that is those which give a breakdown of those risk groups which most closely approximate the patients selected for first-line complete metastasectomy, and those which have buried in them a few cases of complete metastasectomy following immunotherapy.

Throughout this paper the quality of outcome, excellent, good, etc., is given in terms of relative to that expected in MRCC. Papers are referred to by the name of first author.

Conclusions- complete metastasectomy as first-line treatment:

Our main focus has to been to collect the data in such a way that you can draw your own conclusions. However we have had some time to ponder over these results, and if our ownconclusions are of any interest, they are as follows:

The data is limited, and any conclusions are only indicative of what might be confirmed or disproved as a result of further analysis. Within these constraints, as far we can see the published data suggests a number of conclusions which are different to our understanding of the conventional wisdom in the field:

1. The data appears to establish with some strength that attractive outcomes associated with metastasectomy as a first-line treatment **are not confined** to patients with a solitary lung tumor and a longer disease free interval (DFI). As long as the result is **complete metastasectomy of detectable metastases**, it seems that there is a continuum of good or very good outcomes. These start with an outstanding outcome for the best case of complete resection of patients with a solitary lung metastasis and a longer DFI, perhaps typically associated with a 55% survival at 5 years. The outcome degrades by degree as additional risk factors such as multiple metastases and short DFI are added. For patients with one risk factor, that is multiple metastases and a longer DFI, or a single site of metastases and a short DFI, the outcome may typically be 35% survival at 5 years. It seems that the outcomes of these roughly contemporaneous surgical series are surprisingly consistent with each other.

2. Existing data does not answer the question as to whether or not any of these groups of patients would have had a different quality of outcome if they had had immunotherapy as a first line treatment. This uncertainty extends to the best case 'solitary lung/longer DFI' sub-group. However if one had to summarise the position at the moment it would be as follows: for patients with zero or one risk factor (the risk factors being multiple metastases, short DFI), then the position *indicated* is:

> a) There is no data to suggest that these patients would have done better with first-line immunotherapy.
>
> b) The data is consistent with the possibility that these patients would have had a similar outcome with first-line immunotherapy.
>
> c) The data is consistent with the possibility that these patients would have had a significantly less favourable outcome with first-line immunotherapy.

For fully resectable patients with two risk factors the questions would be the same, but the five year survival at perhaps 20% is starting to move the patients into a zone where, for most patients, the morbidity and loss of quality of life from treatment is comparable to the theoretical gain, and less 'toxic' therapies may be more appropriate.

Resolving whether b) or c) is more likely is clearly of major importance to patients.

3. The existing data **does not establish** that good outcomes are only associated with complete metastasectomy confined to lung tumors. The picture is variable and the number of published cases is small, but full resection of evident disease is associated with good outcomes from a number of other sites. For example in Kavolius only 50 of the 96 cases of solitary site complete resections were lung, and yet the overall results of this sub-group were excellent. The general picture that is suggested is that where complete resection to clean margins is possible, it should not be ruled out regardless of the site. In the particularly relevant case of bone sites, there appears to have been little in the way of complete resection. However, in the single largest (but still small) series where reliable eradication of malignant cells has been the goal (Althausen 1997 at Massachusetts General Hospital), the outcome for (presumably complete) resection of bone metastases in the extremities has been a 60% survival at 10 (ten!) years (n=20). Whilst this result may be an outlier, it strongly suggests that the conventional wisdom with regards to bone metastases should be queried.

4. The relatively good results associated with full metastasectomy relate to a programme of continuing resections. Perhaps as many as half of all longer-term survivors in these series will have had two or more metastasectomies.

5. The general view is that the fraction of patients who are eligible of complete metastasectomy is only a few percent. In these retrospective series, there is little specific data. In another paper (O'Dea 1978), a careful reading shows that 13.3% of metastatic patients had a solitary metastasis, and that 8.5% underwent resection The fraction of patients who might benefit is probably increasing as detection of RCC continues to move to an earlier stage in the disease. Expansion in the criteria for treatment to include those with one risk factor, and to include patients with extra-pulmonary metastases would presumably increase the treatable fraction considerably. There is one indirect indication of resectability in carefully followed-up patients: Kierney et al state "More than one third of our SCR patients developed extra-thoracic soft-tissue [re-]recurrence. **All such lesions were amenable to excision**." In the case of complete metastasectomy after biotherapy, in the series

published by Kim et al. (1992) complete metastasectomy was carried out approximately 25% of patients who experienced a PR from biotherapy, and the authors state 'the number of patients who underwent resection probably underestimates number who may be candidates for surgery'.

6. The underlying hypothesis is that resection to below some threshold level of disease will result in a statistically favourable outcome. This threshold is related to that of gross metastases, defined in terms of that which was detectable within the published series. This would suggest that going forward, with evidence now encouraging the determined application of improving techniques of tumor detection, future outcomes would better than that achieved in these historical series.

7. Presumably, as with melanoma, over time the question of complete metastasectomy as a first-line treatment for MRCC should become a question of complete metastasectomy followed by biotherapy.

Conclusions - complete metastasectomy after biotherapy:

1. Actual treatments and published data seem to be very limited, and conclusions must be tentative. Patients treated are largely confined to those who had at some point an objective response to treatment. This included CRs, PRs, in some cases stable disease, and, at least in one series, patients with a mixed response.

2. With these limitations, the consistent indication is that the outcome associated with these patients is excellent, and, as far as can be seen, is as good as (and in some series better than) the outcome for patients who achieved a complete response to biotherapy alone. Although the treatments are not randomised, even allowing for selection, it seems highly likely that these outcomes are as a result of treatment.

3. A relatively large fraction of patients with responses may be eligible for this treatment - Maybe even as many as one third of all responders (Kim 1993). If this quality of outcome is sustained for this number of patients, then the opportunity is there to use this multimodal therapy to roughly double the number of patients who achieve a 'CR' quality outcome from current biotherapy.

4. It would seem appropriate to examine with vigour the question of extending this multimodal approach to all patients post-biotherapy, for whom complete metastasectomy is an available option. We suggest three reasons for this - first of all no compelling rationale has been suggested as to why patients who have failed biotherapy should be worse candidates for complete metastasectomy than equivalent patients who are being treated with complete metastasectomy as a first-line treatment. Secondly the results of histology of resected tumors in these series confirms that biotherapy will often be having an effect which cannot be picked up radiologically. Thus absence of radiological of response at the gross tumor level does not signify a complete absence of response, and in particular does not rule at a benefit from biotherapy in occult tumors. Thirdly, the quality of the outcome from these selected patients appears to be so good that extending the criteria somewhat, to include patients who may be in a higher risk category, still allows for the possibility of good or very good results.

5. The tentative indications of these results suggests that, an updated collation of these cases should be brought together as soon as possible. Based on the five papers we have looked at, this would provide a median follow-up exceeding 60 months in over 60 patients.

Complete metastasectomy as first-line treatment for MRCC - analysis of published data:

immunotherapy

Current practice in the treatment of metastasised renal cell carcinoma (MRCC) is that, in the absence of brain metastases or of a need for acute surgical intervention, in most cases, subject to eligibility, the first choice of treatment is some form of immunotherapy, often as part of a clinical trial.

metastasectomy

The one exception to this is in the treatment of solitary lung metastases. It is generally accepted that where the patient has a solitary and fully resectable lung metastasis, together with adequate performance status, then the treatment of choice should be metastasectomy, particularly if the disease free interval (DFI) is not short.

the critical question

With the publication of a growing number of surgical series, evidence is accumulating that relatively good outcomes are not in fact cut off at the point of metastasectomy of a solitary lung metastasis. In most series, the major determinant of a relatively good result is whether or not the patient underwent resection to a state of no evidence of disease, (SCR) as defined by the scanning protocols that were applied at the time of treatment.

The acceptance of metastasectomy as the procedure of choice for patients with a fully resectable solitary lung metastasis and a longer DFI is not based on data from randomized trials. It has not been established to what extent the outcome is a result of treatment, or of patient selection. Nevertheless the treatment rationale is clear: these patients achieve a probability of survival which is higher than is generally associated with this disease. Thus for eligible patients , choosing to forgo this treatment involves taking the risk of forgoing what might be a substantial survival benefit.

The critical question at this time is how far does this logic in fact extend to a wider range of patients.

In the rest of this paper we will look at particular questions suggested by the pattern of data in the literature. Given the established view that metastasectomy beyond a solitary pulmonary metastasis would have little impact on survival, it is not surprising that the evidence available is quite limited.

the complete metastasectomy hypothesis

The hypothesis that is suggested is that there is an underlying reality that resection to below some threshold level of disease, SCR(threshold), will often result in a favourable outcome, even in the case of patients with metastases at multiple organ sites. This threshold is at or below the level of 'no evidence of disease' as defined by the process of disease detection applied in the published series.

patient selection

As always with relatively good results in MRCC, patient selection is a factor and may account for much of the outcome. Clearly selection bias will have a major impact on the outcome of the patients in the published series who underwent only partial metastasectomy. Thus the critical issue is not to compare the outcomes of these retrospective series in terms of complete resection versus incomplete

resection. The critical question is whether, as a first-line treatment, the outcome for complete resection is better, worse, or the same as would have been the case with immunotherapy.

interpreting historical data

If the SCR(threshold) hypothesis is valid then this raises a number of issues with respect to interpretation of the series published to date. The first is that a significant element of the favourable outcome seen *is* as a result of treatment. The second is that a number of patients in the series who were analysed as SCR will actually have had one or more undetected gross tumors, that is were false-SCR(threshold). Had more of these tumors been detected, the outcomes for the SCR group would have been better, due to reclassification of some patients, and due to extended surgery and thus 'conversion' from false-SCR to true-SCR of other patients.

At the time the treatments in the published series were carried out, there was no evidence to suggest that complete detection and removal of multiple metastases might be so significant, and access to effective scanning technology may have been more limited than at the present time. In most published papers no data is provided on the approach taken to detection, and issues related to limitations on detection are not discussed.

The basis on which patients were selected for complete metastasectomy was different in each series, and the de facto definition of 'no evidence of disease' was probably also quite variable. We have limited the choice of papers examined to those published in 1990 or later, so that many of the treatments occurred during a period when CT scanning was relatively accessible, with the intent that these papers would reflect a level of false-SCR determinations low enough for the analyses to be meaningful. However this is a very crude cut-off, as all papers include long periods in which CT scanning was not generally available, the approach to using scanning was very variable, and most papers give no guide as to what scanning actually took place!

There may be some groups of patients where failure to detect gross metastases was more common, and where consequently more intensive scanning or technical improvements may disproportionately improve outcomes in the future. This may include patients with multiple metastases and patients with axial bone metastases.

The issues related to failure to detect gross metastases apply equally to the question of whether patients are truly 'disease free' after apparently curative nephrectomy.

solitary pulmonary metastases with both long and short DFI

A number of recent series have confirmed that for eligible patients, complete resection of a solitary pulmonary metastasis is associated with an excellent outcome. Broadly speaking the result that has been achieved in the more recent series is of a five year survival of 50%: Friedel 1999 49% n=35; Kavolius 1998 52% n=70; Fourquier 1997 53% n=17; Pastorino (all-cancers) 50% n=819. The Kavolius data is for single organ sites, and includes extra-pulmonary sites. In the Pastorino series only 372 of 5206 cases were kidney cancer. We have included this data because the sheer size of this series provides a credibility check on the results of smaller MRCC series. The relative risk of death for kidney cancer cases in the Pastorino series was 0.93 .

There is to some extent a view at present time that complete metastasectomy should only be the first choice of treatment when the disease free interval (DFI) between nephrectomy and diagnosis of metastases exceeds twelve months. Note however that all the figures given above (except for Pastorino) apply to all patients treated, irrespective of DFI. Looking at the literature, the effect of DFI

is variable, but there clearly is a trend towards better outcomes where the DFI exceeds one or two years.

Looking at the pattern of data in these recent series, it would seem that patients who were treated with a short DFI would be expected to achieve a five year survival of about 30%. As this figure includes patients with both single and multiple metastases, patients with a short DFI and a single metastasis will have achieved a five year survival of somewhere between 30% and 50%, and patients with a single metastasis and a longer DFI will have achieved a five year survival somewhat better than 50%. This would seem to indicate that, where achievable, a complete metastasectomy for a solitary lung metastasis might be the first treatment of choice *regardless of DFI.*

synchronous metastases - not the same as a short DFI?

The reporting of synchronous metastases is variable. In many papers, including the Pastorino series, synchronous metastases are treated as a DFI of 0 and included in the short DFI group. However, as far as we could make out, where synchronous metastases are looked at separately, the pattern that emerges is the rational one, that synchronous metastases are not as negative a factor as short DFI. This would account for the apparently anomalous result in the Pastorino series that patients with a DFI of 0-11 months fared slightly *better* than patients in the next DFI category (33% of patients in the Pastorino 0-11 month DFI group had synchronous metastases).

multiple metastases/multiple sites of metastases, with long DFI

There is relatively limited data on this question, which is not surprising given the conventional wisdom in effect, and given the relative abundance of pulmonary metastases in MRCC. In the Kavolius series the five-year survival of 47 patients with multiple sites of metastases was 29%. The figure for Friedel 1999 was 19%, and for Fourquier 1997 53%. In the large Pastorino all-cancer series , patients with complete resection of multiple metastases had a 5 year survival of approximately 34% , compared to approximately 45% for patients with a single metastasis. All these figures were for all patients with multiple metastases, irrespective of DFI. Thus as a best estimate one would expect the outcome for eligible patients for a reasonable number (say n=5) of metastases and a long DFI to be equivalent to a risk score of one, with a five year survival of about 30%. Again this might be better than one might associate with other treatments.

The data on complete resection of multiple metastases in MRCC becomes more limited as the number of metastases increases. The general pattern of existing data would suggest that the outcomes discussed here are valid up to perhaps 5 metastases, with a general worsening as the number of metastases increases. The useful limit with lung metastases may be higher, and pre-operative CT staging may on occasion exclude treatment erroneously by overestimating the number of pulmonary tumors. For example in Pogrebniak 1997, an average of six nodules (range 1 to 19) were resected, but only half of these were RCC tumors.

multiple metastases with short DFI

Looking at the pattern of data in the published series, eligible patients with both multiple metastases and a short DFI would be placed in a group with two significant risk factors. Looking at the data, one might estimate that the outcome based on the general approach reflected in these papers would be a five year survival of approximately 20%. Whilst this may still be in the range of results of the lower risk quartiles in many immunotherapy series, the outcome is such that the potential benefit associated with complete metastasectomy is limited.

Complete metastasectomy or immunotherapy?

The data sets available are not conclusive. On the one hand the results of complete metastasectomy may simply be a question of patient selection. Of all MRCC groups, cases with a fully resectable lung metastasis, a longer DFI, and excellent performance status will presumably fall into the lowest risk group of patients, and might regularly have achieved the >70% three year survival and >50% five year survival whatever treatment is considered. On the other hand, the best risk quartile of patients qualifying for IL-2 based immunotherapy during the treatment period being analysed may also largely consist of patients with excellent performance status and solitary metastases. More data is available for this group than we have been able to tabulate. However the general pattern for this group would appear to be a three year survival of 40%. If indeed these two groups are comparable, then there is a substantial advantage in favour of a 'programme' of complete resection, with a highest conceivable relative benefit of perhaps a doubling of three year survival. Thus from the patient perspective, in these cases there is up to a factor of two uncertainty in the relative benefit of complete metastasectomy versus immunotherapy.

What is established beyond reasonable doubt from these surgical series, is that the outcome for complete metastasectomy of a solitary lung metastasis in MRCC is not an exceptional result. What is established is that, for patients who have undergone apparently complete resection of metastases, there is a continuum of outcomes. This starts with an excellent outcome, perhaps a five year survival of 60%, for eligible patients with a solitary metastasis (not necessarily even restricted to lung metastases - see below) and a longer DFI, and then degrades smoothly as risk factors mount.

What this implies is that if there is indeed a substantial survival benefit in favour of complete metastasectomy for patients with a solitary lung metastasis, then it is quite possible that the relative benefit applies to many more patients, and is likely to include those with a Pastorino risk score of 1.

Resolving this uncertainty is clearly very important to patients.

non-pulmonary sites

A proper examination of the data on non-lung sites would require a major exercise for each site of metastasis. However there is one thing that seems fairly clear. The data does not support the conclusion that good outcomes are only regularly associated with lung metastases. On the contrary, the tentative conclusion is that metastasectomy with the intent of complete resection carried with diligence can produce good results in many types of tumors, and apparently useful results even in some of the most infamous sites. The limited data available here suggests that the conventional wisdom relating complete metastasectomy exclusively to lung metastases may be inadvertently denying many patients the chance of a good or excellent outcome.

bone metastases

After the lung, the most frequent site for metastases in MRCC is bone. There are few published reports of attempts at complete resection of bone metastases in MRCC. A notable exception to this is Althausen et al 1997. At the Massachusetts General Hospital an exceptionally aggressive approach has been taken to resection of bone metastases in MRCC, with survival outcomes similar to that for lung tumors. In a population of 38 patients with bone metastases the overall outcome was a five year survival of 55% and a ten year survival of 39%. In our reading, it is not absolutely clear from the paper if these were complete resections, but the quality of outcome suggests that this is likely to have been the case. Their results were even better for the subset of patients with non-axial bone metastases,

with a five year survival of 75%, and a ten year survival of 60% (starting n=20). With ever improving instrumentation, resection of bone tumors can increasingly be achieved without amputation.

Althausen et al found that about half of the patients with axial metastases died in the first two years, and then the rate of death reduced dramatically. Looking at their data, it would seem that these early mortality axial metastasis patients all had a short DFI (<2 years in their terms). Given that many axial metastases are non-symptomatic (Lekovsky, personal communication), and given the difficulty of detecting axial metastases (see below), one might speculate that many of the patients with these metastases actually had gross axial metastases at the time of their nephrectomy. It would seem that to determine the true situation would require an MRI of the spine. If the Althausen experience is repeated elsewhere, it would seem appropriate to treat axial and extremity bone metastases in MRCC as two separate groups.

Others, perhaps taking less aggressive approaches, have achieved less impressive results. In the series analysed here, Kavolius reported a five year survival of 40% in five patients with complete resection of a solitary bone metastasis. Dürr, in a series where most patients were not completely resected, reported a five year survival of 54% in patients (not necessarily SCR) with a solitary bone metastasis and a DFI of more than 12 months.

A particular problem with axial bone metastases may be that of reliability of tumor detection. In a comparison between conventional whole-body scintilography (RNB) with 18F PET (Schirrmeister et al. 2000), it was found that RNB only detected 48% of 96 bone tumors detected by 18F PET (in 44 patients with known prostate, lung and thyroid carcinoma). RNB detected only 40% of bone metastases in the spine and pelvis, as opposed to 83% of bone metastases in other areas.

non-pulmonary metastases summary

Excluding brain, there were 25 cases of complete resection of single site non-pulmonary metastases, and 50 cases of complete resection of single site pulmonary metastases in Kavolius 1998. The overall outcome for these non-pulmonary cases was marginally better than for the pulmonary cases. Taking this together with the data from Althausen appears to show that, other than for brain, liver and axial bone metastases, where complete metastasectomy has been applied to non-pulmonary metastases, the outcome has been similar to that associated with complete metastasectomy of pulmonary metastases.

Complete metastasectomy following limited or unsustained response to biotherapy:

Subject to the limitations of small series and very limited follow-up, the outcome is consistently excellent. It looks as if the outcome for these patients will be the same as if they had a complete response to biotherapy alone. An explanation for this is suggested by the histology. The condition of resected tumors ranges over the whole spectrum from complete free of viable malignant cells, to almost unaffected by biotherapy. However many of the tumors consist mainly of necrotic tissue with small foci of malignant cells. It is generally accepted that gross tumors are very heterogeneous in a number of ways. This is seem as a barrier to reliable penetration of all areas by an adequate concentration of therapeutic agents, and may also possibly be a barrier to effective access by relevant cells of the immune system. This problem may be worse for large detectable tumors than it is for small occult micrometastases. Equally, tumors are associated with both chemokine and cellular factors which inhibit immune attack. These factors may also be more concentrated and more difficult to overcome in larger tumors. Thus the logic may be that in some patients, biotherapy has been

effective in eradicating or substantially diminishing occult disease, even if malignant cells cannot be completely eradicated in gross tumors. This would explain a beneficial outcome of resection of all detectable metastases.

Some of the good outcome of this group is likely to be associated with patient selection. These patients will have had good performance status, sustained through the period of biotherapy. However, selection of good performance patients will to some extent apply to all responding patients, and it seems likely that much of the quality of the outcome is as a result of the additional treatment.

Looking forward:

What might be done in light of this emerging data? The following issues would seem to be some candidates for consideration:

resolving the issue of relative benefit of complete metastasectomy versus immunotherapy as s the first line of treatment

A randomised trial is always a desirable but an unlikely option in MRCC. What else can be done which, although a compromise, will further inform judgement? It would seem to us that a possible route is to take advantage of the fact that many centres have ongoing or completed immunotherapy trials. On the whole, patients who would qualify for complete resection would also qualify for immunotherapy. Thus there are likely to have been, and continue to be, a number of patients on immunotherapy trials who would have qualified for complete resection. It would seem useful to try to identify these cases and to see what the outcome has been on immunotherapy. There would be significant benefit in this analysis, even if it were restricted to the simpler categories, such as solitary lung metastases.

improving information on surgical history

Relevant surgical series are few and far between. There would appear to be a number of possible ways of improving our knowledge, based on work already carried out. Major centres might be encouraged to carry out further retrospective analyses. Some of the authors of work already published might be encouraged to expand their analysis. Where follow-up was short at the time of writing, authors might be encouraged to update the key data. A separate analysis of kidney cancer cases in the International Registry of Lung Metastases might be commissioned. There were 372 kidney cancer cases in this database in 1997, so the number of MRCC cases available to analyse should now be even larger.

surgical series going forward

No doubt complete metastasectomy as the first line of treatment will continue to take place. Going forward, the existing papers suggest a number of developments. The main issue is the apparent benefit of complete resection versus incomplete resection. This would suggest an increased value in relatively intensive pre-operative and intra-operative detection of tumors, both to improve outcomes in some cases, and to avoid surgery without benefit in other cases. It would be useful to see some work done to establish further the conditions under which MRI of the spine would make a useful contribution to proper staging. The other key issue which emerges is the need for, and benefit of, re-resection in about half of longer term survivors, and better results are likely to result if this is contemplated from the beginning. It is possible that some of the emerging minimally invasive

techniques of tumor ablation, such as stereotactic radio surgery may make subsequent metastasectomies more acceptable and appropriate.

Biotherapy-lead multimodal trials and treatments:

As already discussed, it would seem of significant importance to patients to substantially expand the frequency with which complete metastasectomy following biotherapy is an inherent part of the treatment or of the trial, as well as expanding the category of patients who participate.

Metastasectomy-lead multimodal treatment and trials:

This question merits a paper of its own. However we suggest three reasons why biotherapy consequent to complete metastasectomy should become the norm in RCC: firstly, there is clearly a need to reduce the level of further recurrence; secondly there are a number of scientific reasons to hypothesise that, in general, complete resection to the level of occult disease may result in a more favourable environment for biotherapy. Morton (Morton 1999) has described 'cytoreductive surgery as a form of immunotherapy'; and thirdly, in melanoma there is emerging evidence that some tumor-based vaccines may be particularly effective after complete metastasectomy.

Appendix 1: Role of Metastasectomy in MRCC - Survival Data

In order to provide comparable measurements, much of the data is taken off Kaplan-Meier diagrams and is approximate. Where it is clear that the number of patients involved was much too low for a reliable result, the data is in *italics*. If the number of patients at risk appeared to be so small as to render the data meaningless, then no data is given. SCR denotes metastasectomy to no evidence of disease, as detected at the time, SPR denotes metastasectomy with evident disease remaining.

The risk score follows the suggestion of Pastorino et al: Individual risk factors are; multiple metastases; a short DFI. The risk score corresponds to the number of these risk factors (0, 1 or 2). Palmer in addition has an EOCG of 1 (as opposed to 0) as an additional risk factor. Presumably this was not a significant issue in most of the surgical series as patients eligible for surgery would mainly have had an EOCG of 0. Papers are listed in reverse date order

Survival by category:

Metastasectomy as first-line treatment:

	median:					initial n:	
Risk score 0 - '0.5'							
(Note that for Kavolius, Fourquier and Freidel, the groupings will include a mixture of patients with 0 and 1 risk factors)							
Freidel 1999 SCR lung solitary	48 months	2 y 70%	3 y 60%	5 y 49%	*10 y 35%*	35	
Kavolius 1998 SCR single site	70 months	2 y 78%	3 y 65%	5 y 52%		94	
Kavolius 1998 SCR single site lung				5 y 54%		?	
Fourquier 1997 SCR lung solitary	36 months	2 y 53%	*3 y 50%*	*5 y 26%*		17	multiple *better* (*)
Freidel 1999 SCR lung DFI> 48 months	58 months	2 y 72%	3 y 55%	5 y 46%	10 y 40%	27	
Kavolius 1998 SCR DFI >12 months	65 months	2 y 75%	3 y 70%	5 y 53%		71	
Kavolius 1998 SCR bone solitary				*5 y 40%*		*5*	very low n
Pastorino 1997 SCR risk score 0 (all cancers)	61 months	2 y 73%	3 y 65%	5 y 50%		819	

(*) The difference was not statistically significant, but we still found it surprising that it favoured multiple. It is even possible the graph was mislabelled though we have no evidence this is so.

Risk score 1 - '1.5'
(note that for Kavolius, Fourquier and Freidel, the groupings will include a mixture of patients with 1 and 2 risk factors)

Kavolius 1998 SCR multiple site	30 months	2 y 60%	3 y 50%	5 y 29%		47	
Fourquier 1997 SCR multiple - largely lung	84 months	2 y 70%	3 y 67%	5 y 53%		28	multiple *better*
Freidel 1999 SCR lung multiple	36 months	2 y 70%	3 y 40%	5 y 19%	*10 y 10%*	42	
Freidel 1999 SCR lung DFI < 48 months	32 months	2 y 65%	3 y 40%	5 y 26%	*10 y 20%*	50	
Kavolius 1998 SCR DFI <12 months	24 months	2 y 50%	3 y 42%	5 y 33%		70	
van der Poel 1999 SCR (here due to mix)	35 months	2 y 60%	3 y 50%	5 y 29%		55	risk score ?
Pastorino 1997 SCR risk score 1(all cancers)	34 months	2 y 61%	3 y 55%	5 y 34%		1720	
Risk score 2							
Pastorino 1997 SCR risk score 2 (all cancers)	24 months	2 y 50%	3 y 40%	5 y 25%		1553	

Metastasectomy as first-line treatment involving bone:

Althausen 1997 bone total	72 months	2 y 65%	3 y 55%	5 y 55%	10 y 39%	38	
Althausen 1997 bone multiple	36 months	2 y 62%	3 y 50%	5 y 35%	10 y 25%	26	
Althausen 1997 bone extremities			2 y 80%	5 y 75%	*10 y 60%*	20	
Althausen 1997 bone axial			2 y 40%	5 y 30%	*10 y 15%*	18	
Dürr 1999 bone solitary & DFI > 12 months				*5 y 54%*		9	

Non - surgical series, for comparison, including best/most selective results:

Motzer 1999 lowest risk quartile overall	20 months	2 y 45%	3 y 31%			167	
Motzer 1999 lowest risk cat. & immunotherapy	26 months					?	
Motzer 1999 lowest risk cat. EOCG IFN-a trial	29 months					?	
Dutcher 1997 all patients HD IL-2	15 months					71	
Dutcher 1997 all patients IL-2 & IFN-a	20 months					47	
Cittero 1997 lung only	24 months					38	
Hänninen 1996 lowest risk IL -2/IFN-a/5-FU 51 of 120 pts		2 y 75%				51	
Fossa 1994 lowest risk, IFN-a group (50% of pts)	24 months	2 y 50%	3 y 40%			71	
Palmer 1992 risk score 0	28 months	2 y 69%	*3 y 42%*			20	few at risk
Palmer 1992 risk score 1	17 months	2 y 42%	*3 y 34%*			99	
Palmer 1992 risk score 2	10 months	2 y 11%				129	

Palmer 1992 risk score 3	5 months	79

Complete metastasectomy post-biotherapy:

Dutcher 2000 SCR	>50 months		3 y >75%			8
Krishnamurthi 1998			3 y 81%			14
Sella 1993 SCR - no data - follow-up too short						17
Kim 1992 SCR		2 y 100%	*3 y 100%*			11
Pogrebniak 1992 SCR	>60 months					15

Individual Papers:

MRCC metastasectomy general sites and lung:

van der Poel 1999 **' Metastasectomy in RCC: A multicentre retrospective analysis'**
Holland not lung-specific - many non-lung patients

van der Poel 1999 SCR all	35 months	2 y 60%	3 y 50%	5 y 29%		55
van der Poel 1999 SPR all	12 months	2 y 30%	3 y 20%	5 y 15%		40

Freidel 1999 **'Resection of pulmonary metastases from RCC'**
Germany exclusively lung and SCR

Freidel 1999 SCR lung only	37 months	2 y 65%	3 y 52%	5 y 39%	10 y 21%	77
Freidel 1999 SCR lung solitary	48 months	2 y 70%	3 y 60%	5 y 49%	*10 y 35%*	35
Freidel 1999 SCR lung multiple	36 months	2 y 70%	3 y 40%	5 y 19%	*10 y 10%*	42
Freidel 1999 SCR lung DFI > 48 months	58 months	2 y 72%	3 y 55%	5 y 46%	10 y 40%	27
Freidel 1999 SCR lung DFI < 48 months	32 months	2 y 65%	3 y 40%	5 y 26%	*10 y 20%*	50

Kavolius 1998 **'Resection of metastatic RCC'**
MSKCC not lung specific

Kavolius 1998 SCR all	50 months	2 y 70%	3 y 60%	5 y 44%		141
Kavolius 1998 SCR single site	70 months	2 y 78%	3 y 65%	5 y 52%		94 only 50 lung
Kavolius 1998 SCR multiple site	30 months	2 y 60%	3 y 50%	5 y 29%		47
Kavolius 1998 SCR Lung only				5 y 54%		?
Kavolius 1998 SCR DFI >12 months	65 months	2 y 75%	3 y 70%	5 y 53%		71
Kavolius 1998 SCR DFI <12 months	24 months	2 y 50%	3 y 42%	5 y 33%		70
Kavolius 1998 SPR all	22 months	2 y 45%	3 y 40%	5 y 14%		70
Kavolius 1998 SCR single site bone				5 y 40%		5
Kavolius 1998 single site glandular				5 y 63%		15
Kavolius 1998 single site soft tissue				5 y 75%		5
Kavolius 1998 single site brain				5 y 18%		11

Fourquier 1997 **'Lung metastases of RCC: results of surgical resection'**
France all pulmonary patients

Fourquier 1997 SCR largely lung	48 months	2 y 65%	3 y 60%	5 y 44%	45	
Fourquier 1997 SCR lung solitary	36 months	2 y 53%	*3 y 50%*	*5 y 26*	17	
Fourquier 1997 SCR multiple - largely lung	84 months	2 y 70%	3 y 67%	5 y 53%	28	multiple *better*
Fourquier 1997 SPR largely lung	*24 months*	*2 y 40%*	*3 y 20%*	*5 y 20%*	*5*	very low

Takashi 1995 **'Surgical treatment of RCC metastases: prognostic significance'**
Nagoya not lung specific - brain, bone, lung

Takashi 1995 SCR all	*>72 months*	*2 y 60%*	*3 y 60%*	*5 y 60%*	*10*	very low
Takashi 1995SPR all	*5 months*	*2 y 18%*	*3 y 0%*	*5 y 0%*	*6*	very low

Kierney 1993 **'Surgeon's role in the management of solitary RCC metastases occurring subsequent to initial curative nephrectomy: an institutional review'**
Mayo Clinic not lung specific

Kierney 1993 SCR all (23 single 13 multiple)	41 months	2 y 75%	3 y 58%	5 y 31%	36	
Kierney 1993 SCR intrathoracic			3 y 50%		18	
Kierney 1993 SCR intracranial			*3 y 44%*		6	
Kierney 1993 SCR other			3 y 81%		12	
Kierney 1993 SPR all	*16 months*				5	very low

Tobisu 1990 **'Surgical treatment of metastatic RCC'**
Tokyo not lung specific - some non-pulmonary

Tobisu SCR post-neph metastasectomy?			3 y 47%	5 y 29%	28	

Tobisu SPR post-neph metastasectomy?			3 y 0%				11
Tobisu SCR synchronous metastasectomy?	96 months	2 y 70%	3 y 49%	5 y 40%			18 selected?
Tobisu SPR synchronous metastasectomy?	7 months	2 y 20%	3 y 16%	5 y 16%			16

MRCC metastasectomy bone:

Dürr 1999 'Surgical treatment of osseous metastases in patients with RCC'
Munich All include bone

Dürr 1999 bone solitary (mainly only palliative)	26 months	2 y 60%	3 y 40%	5 y 28%		19
Dürr 1999 bone solitary & DFI > 12 months				*5 y 54%*		9

Althausen 1997 'Prognostic factors and surgical treatment of osseous metastases secondary to RCC'
Massachusetts General - all bone

Althausen 1997 bone total	72 months	2 y 65%	3 y 55%	5 y 55%	10 y 39%	38
Althausen 1997 bone multiple	36 months	2 y 62%	3 y 50%	5 y 35%	10 y 25%	26
Althausen 1997 bone extremities		2 y 80%		5 y 75%	*10 y 60%*	20
Althausen 1997 bone axial		2 y 40%		5 y 30%	*10 y 15%*	18

MRCC complete metastasectomy after immunotherapy:

Dutcher 2000 'Phase II trial of Il-2 & IFN-a & 5FU in MRCC; a CWG study'
multicentre USA median follow-up of this subset not given

Dutcher 2000 SCR (6/8 alive at 43+ - 53+ months)	>50 months (approx)		3 y >75%	8

Krishnamurthi 1998 'Efficacy of multimodal therapy in advanced RCC'
Cleveland Clinic Foundation; mean follow-up 43 months

Sella 1993 'Surgery following response to IFN-a-based therapy for residual RCC'
MDACC median follow-up 12 months

Sella 1993 SCR (8 at risk at 2 years)		*2 y 85%*		17

Pogrebniak 1992 'RCC: Resection of solitary and multiple metastases'
NCI 78% IL-2 based immunotherapy median follow-up 32 months

Pogrebniak 1992 SCR	>60 months	*2 y 70%*		15
Pogrebniak 1992 SPR	16 months	*2 y 30%*		8
Krishnamurthi 1998 SCR			3 y 81%	14

Kim 1992 'Surgical Resection following IL-2 therapy for MRCC prolongs remission'
multi-centre USA; median follow-up 21 months

Kim 1992		2 y 100%	3 y 100%	11

Sherry 1992 'Surgical Resection of MRCC and Melanoma after response to IL-2 based immunotherapy'
NCI follow-up too short for any figures (only 3 SCR patients at risk at 2 years)

Sherry 1992 SCR	12

Immunotherapy:

Motzer 1999 'Survival and prognostic stratification of 670 patients with MRCC' MSKCC

Motzer 1999 lowest risk quartile overall	20 months	2 y 45%	3 y 31%	167	
Motzer 1999 Immunotherapy lowest risk	26 months			?	
Motzer 1999 low risk category on EOCG IFN trial	29 months			?	

Dutcher 1997 'IL-2 based therapies: CWG experience 1989 - 1997'

Dutcher 1997 all patients HD IL-2	15 months			71	
Dutcher 1997 all patients IL-2 & IFN-a	20 months			47	

Palmer 1992 'Prognostic factors in MRCC treated with IL-2'. Europe 327 patients

Palmer 1992 risk score 0	28 months	2 y 70%	*3 y 42%*	20	few at risk
Palmer 1992 risk score 1	17 months	2 y 42%	*3 y 34%*	99	

Palmer 1992 risk score 2	10 months	2 y 10%		129
Palmer 1992 risk score 3	5 months			79

Fossa 1994 'Prognostic factors and survival in patients with MRCC treated with chemo or IFN-a' Norway

Fossa 1994 lowest risk, IFN-a group (50% of pts)	24 months	2 y 50%	3 y 40%	71

Hänninen 1996 'IL-2 based home therapy of MRCC: risk and benefit in 215 consecutive single institution patients Germany

Hänninen 1996 lowest risk grp of IL-2/IFN-a/5-FU 51 of 120 pts		2 y 75%		51

Appendix 2 - Notes on papers in alphabetical order:

bCR, bPR denote biotherapy induced CR and PR etc..

Althousen 1997: - in their cohort, the curve of non- axial metastases was very flat. The curve for axial metastases was very steep for two years, and then flattened out remarkably. This may suggest that there are two subgr oups within this axial cohort; 5 of the 38 patients did not receive nephrectomy - 3 declined, two had chemotherapy only. 17 patients were synchronous.

Dürr 1999; Munich; Retrospective review of a series of 45 consecutive patients treated surgically for solitary or multiple metastases to the bone; Treatments occurred form September 1980 to January 1998; Sites: Spine (15 patients), Pelvis (8), femur (11); All patients presented with pain, five had neurologic impairment, four had a fracture; No analyses of SCR patients; a wide or radical resection was only undertaken in 7 out of 45 patients. In the other 38 patients, a palliative or diagnostic procedure was carried out.

Dutcher 2000: 2 CRs (5 and 53+ months) and 7 PRs on IL-2 based biotherapy; after one course, 8 MRCC SCR - from 3 bPR, 1 bMR, 4 bSD; 6/8 alive at 43+ to 53+ ; 4 disease free since SCR; SCRs are 6 out of eight total survivors on the trial.

Fossa 1994: - 295 MRCC pts. treated with chemo 1975-1990 or IFN-a 1983 - 1990. 159 chemo, 136 IFN -a; Lowest risk group IFN-a group survivals from diagrams - median 24 months, 2 year 50%, 3 year 40%. This was 71 out of 136 IFN-a patients, i.e. 50% of this group.

Fourquier 1997; France; 50 consecutive patients treated 1960 to 1994 with pulmonary resection of metastases arising from RCC; 5 of these patients had had previous immunotherapy without significant response; Mean age 58 years (40-78); All patients had a radical nephrectomy; 8 patients had synchronous pulmonary metastases, 42 had metachronous metastases; For patients operated on "in the last fifteen years" thoracic, brain, and abdominal CT -scans were systematically performed; "During the surgical procedure, the lung should be palpated very carefully in order to find unexpected nodules. Thorascopy has been used to resect metastatic nodules. We believe that this procedure should be limited to diagnosis because it is not possible, by this procedure, to explore the lung completely and safely in order to search for micronodules which were not identified by CT -scan, and finally to perform regularly a curative resection."

Freidel 1999: - SCR effect of multiple mets and of short DFI seen mainly at longer intervals (5 years); SCR unilateral no different to bilateral (as a univariant factor)

Hänninen 1996: 215 pts. Three IL-2 based regimes. Lowest risk best performing group - (51 out of 120) pts. 2 year survival approx 75%.

Kavolius 1998: - Retrospective review of 320 patients with diagnosis of recurrent or metastatic RCC at MSKCC. Only those referred to the department of surgery were reviewed; 129 (40%) of patients had evidence of distant metastases at time of original diagnosis. 42 patients did not undergo nephrectomy. These are excluded form analysis; 278 patients who received a curative nephrectomy were diagnosed with recurrent or metastatic disease from 1980 to 1993; 141 patients were rendered SCR at first recurrence, 70 patients SPR. Occurrence defined as solitary if only renal bed, one organ site, or unilaterally in lung; Previous treatment: 31 of the 278 patents had additional therapy at the time of nephrectomy including chemotherapy, biotherapy and radiotherapy. No data or other comment is given in the paper with respect to the practice followed for detecting metastases; 53 of 278 patients had bone tumors. No analysis is given of how many of these were in the 141 SCR patients group. Only Five patents in the SCR group had a solitary bone metastasis.

Kierney 1994; Mayo Clinic; Retrospective review of 454 patients with metastatic RCC between 1970 and 1990; Selection criteria - nephrectomy and/or apparently solitary metastasectomy at Mayo; Patients with **skeletal, spinal cord, lymph node metastases excluded**; 41 patients with metastasised RCC meeting criteria; Metastasectomy of isolated second metastasis was a criterion for re-operation; 36 patients SCR, 23 solitary, 13 multiple metastases; 5 patients SPR; 13 of 36 SCR patients underwent second curative resection - 11CR; 4 of 11 had multiple excisions. One patient had three curative resections, and one patient 12; 18 of 36 SCR patients had some form of subsequent adjuvant therapy; The sole statistically significant predictor of survival was that of increased tumor gr ade of the resected metastatic lesion relative to the original tumor: median survival of 22 patients with no increase in tumor grade: 4.5 years; median survival of 14 patients with increased tumor grade: 2.3 years; "More than one third of our SCR patients developed extra-thoracic soft - tissue recurrence. **All such lesions were amenable to excision** ."

Kim 1992: retrospective review of 14 prospective clinical trials involving IL-2 or LAK cells; Some patients who had BPR or BCR (with recurrence) were rendered SCR though surgery, there were no guidelines specifying criteria; 269 Il-2, 130 LAK; 11 rendered SCR; from 10 BPR and 1 BCR of a total population of 44 PR and 17 CR (of whom not specified how many progressed subsequently; **(MDF note: this is about 1/4th of all PR patients)**; All SCR patients were EOCG 0; 'surgery often facilitated by reductions in tumor size induced by IL-2 therapy; Overall survival and disease-free survival of SCR patients is 100% at time of writing; Histology: **61% of patients had large intra-abdominal tumors**. 'number of patients who underwent resection probably underestimates number who may be candidates for surgery'; Histology ranged from tumors free of malignant cells, to tumors with small microscopic foci, to grossly viable tumor with minimal secondary changes.

Krishnamurthi 1998: 1988 to 1996, 14 MRCC patients rendered SCR; All had objective response or stable disease, were apparently fully resectable, and had EOCG of 0 or 1 and only such patients were selected for surgery; Mean age 55.7 years; 8 of 14 had had prior nephrectomy; 1 BCR, 2 BPR, 3 BMR; 3 Bmixed response, 5 stable disease; Mean follow-up 22 months; 7 of 14 have undergone re-resections; Cancer specific survival is 81% at 3 years. 7 patients NED at mean follow-up of 48.3 months. Numbers are small but 5 of 8 patients with prior nephrectomy are NED compared to 2 of 6 patients who had had primary in place as well as distal metastases, but follow-ups are short at approx 40 months.

Motzer 1999: - 670 MRCC patients on MSKCC trials 1975-1996. Median 10 months. 2 year 20%, 3 year 11%; best quartile of patients median survival 20 months, 2 year 45% 3 year survival 31%.. Immunotherapy lowest risk group median 26 months

Pastorino 1997: DFI data - Pastorino have classified synchronous metastases as a DFI of 0, and are included in the short (0-11 month) category. This may explain the oddity that their (0-11 month) group fared better than the (12-35 month) group. If synchronous MRCC patients were excluded for the (0-11 month DFI group), other data suggests that their short DFI group would have had a worse outcome than their other DFI groups; All patients who underwent lung metastasectomy with curative intent were eligible; Eradication of primary and effective treatment or absence of metastases in other organs was a requirement; 5206 patients, of which 4572 were SCR; 46% were single metastases, 26% two to three metastases, 26% four or more metastases; Analysis presented is for all patients; **372 patients had a primary in the kidney**. However relative risk of death for kidney cancer patients was 0.93; All figures given below are for complete population; A further occurrence was documented in 56% of SCR patients, Median time to recurrence 10 months. Long term outcome of this group was good - 5 years survival of 44%, ten year survival 29%; "Radiological staging of lung metastases was inaccurate in a large proportion of cases and intra-operative exploration by an experienced surgeon is required to optimise resection of all metastases. In this respect video-assisted thoracopy cannot provide optimal intra-operative identification of pulmonary metastases, particularly when more than one lesion is identified in the preoperative period."; Overall, the radiologic detection of the number of lung metastases was accurate in 61% of patients, underestimated in 25% and overestimated in 14%. For the subset of patients who underwent monolateral thoracotomy underestimation occurred in 16% of cases and overestimation in 8%. In those patients who had median sternotomy or bilateral thoracotomy, there was underestimation in 39% and overestimated in 25%, of cases.

Pogreniak 1997: 23 pts 1985 - 1991. 15 MRCC SCR; 8 others not resectable. 18 of 23 had previously received IL-2. Short follow up.

Sella 1993: 1987 to 1990, review of 17 MRCC patients; Sites: 10 lung, 6 lymph nodes, 2 liver, 1 bone, 8 primary; 16/17 had bPR, 1 bMR; of 8 patients presenting with primary in place, 6 had bCR of metastatic disease (5 lung); Follow-up is short - median 12 months; Survival is 85 % at two years post-operatively , with 8 patients at risk at this point. 15 out of 17 patients (88%) had viable malignant cells in their resections. This occurred in 64% of lung nodules and 13% of lymph nodes. (MDF note - as some lung nodules and lymph nodes originally picked up on staging are not tumors, the percentage of tumor masses which were originally malignant and which still contain malignant ells on resection is likely to have been higher than this). Sella et al note that the hypothesis of full metastasectomy following some response to biotherapy was being prospectively evaluated at MDACC as of time of writing (1993) - and this appears still to be the case as of 2002 - according to the MDACC RCC treatment flow chart.

Sherry 1992 : 1984 to 1990 424 patients with MRCC or metastatic melanoma on one of four IL-2 based protocols; 16 MRCC Patients with limited relapse or persistent disease after PR or CR resected; median time to progression after resection 11 months; Patients resected where all *relapsing sites* of tumor could be resected. *Sites where durable partial response typically not resected*. 12 of 16 SCR; 10 of these 12 alive at time of writing, 6 with NED; survival at 2 year 65% (MDF construction of Kaplan-Meier table), but SCR n at this point only 3.

Tanguay 1996: 1981 to 1992 51 patients metastasectomy to lung for RCC at MDACC; 29 after biotherapy, metastasectomy as 1st line treatment for 22; all but 4 patients had had nephrectomy; 46 SCR of 51 total; re-recurrence occurred in 38 of 46; and in 12 of these 38 re-resection , 5SCR and 7 SPR; No survival data given for 46 SCR patients.

van der Poel 1999: Series is 101 pts, 1983 to 1992, multi-centre, Holland. Analysis of 95 patients who had nephrectomy. Paper submitted 1997 so approximately 60 months minimum follow-up. Selection basis for retrospective analysis was that patient had to have had at least one metastasectomy, whether synchronous or asynchronous; 56 patients SCR, 39 SPR; All survival figures are disease specific; "Preoperative screening for the presence of other metastases varied amongst patients. In all patients a chest x-ray was performed. A bone scan and CT scanning of the abdomen, chest, or cerebrum were only performed when symptoms or earlier investigation suggested lesions in these areas."; no sub-group analysis of SCR patients.

Appendix 3 - table of papers analysed:

Papers:

In reverse date order.

MRCC metastasectomy papers analysed:

Van der Poel	1999	55 SCR	no subgroup analysis of SCR patients	Holland
Friedel	1999	77 SCR	exclusively lung	Germany
Dürr	1999	45	bone - no SCR analysis	Munich
Kavolius	1998	141 SCR	general	MSKCC
Fourquier	1997	45 SCR	lung-centric	France
Althausen	1997	38	bone only - no SCR analysis	Massachusetts
Takashi	1995	10 SCR	limited data - few patients	Nagoya
Kierney	1994	36 SCR		Mayo Clinic
Tobisu	1990	50 SCR	difficult groupings	Tokyo

MRCC complete metastasectomy post-immunotherapy analysed:

Dutcher	2000	8 SCR	post-immunotherapy	multicentre USA
Krishnamurthi	1998	14 SCR	post-immunotherapy	Cleveland Clinic Foundation
Sella	1993	17 SCR	post-immunotherapy	MDACC
Pogrebniak	1992	15 SCR	various	NCI
Kim	1992	11 pts	post-IL-2 immunotherapy	multicentre USA

non-MRCC metastasectomy analysed:

Pastorino	1997	4572 SCR	lung - various cancers	international

MRCC prognosis / immunotherapy analysed:

Motzer	1999	670	IFN-a & IL-2 & various	MSKCC
Dutcher	1997		IL2: CWG experience 1989-1997	CWG
Hänninen	1996	215	Il-2 & various	Hannover
Cittero	1997	109	various non-surgical therapies	Milan
Fossa	1994	295	IFN-a & chemo	Norway
Palmer	1992	327	IL-2 CIV	European

MRCC read and data not included in tables:

Tanguay	1996	46 SCR	no survival data given for SCR sub-set	MDACC
Cozzoli	1995		lung - not enough data	
Tongaonkar	1992	21	not enough data	India
Thrasher	1990		too few patients	Army
Katzner	1990	40	bone - not curative, no survival data	Strasbourg
Witz	1990	17 SCR?	no CT? intrathoracic	Strasbourg
King	1990		spine - non curative	
Jett	1983	44 pts	too early	Mayo Clinic
O'Dea	1978	28 pts	too early	
Tolia	1975		too early	

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