Prospective Controlled Cohort Studies on Long-Term Therapy of Cervical Cancer Patients with a Mistletoe Preparation (Iscador®)

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Key Words
Cervical cancer · Metastases · Survival · Quality of life · Complementary and alternative medicine · Anthroposophic medicine · Mistletoe · Iscador

Summary
Background: Mistletoe preparations such as Iscador are commonly used in complementary medication for many cancer indications, particularly solid cancers. The efficacy of this complementary therapy is still controversial. Objective: Does long-term therapy with Iscador show any effect on survival, tumor progression and psychosomatic self-regulation of patients with cervical cancer? Patients and Methods: Prospective recruitment and long-term follow-up was carried out in 3 controlled cohort studies: In a randomized matched-pair study (19 pairs), cervical cancer patients with distant metastases and no mistletoe therapy were matched for prognostic factors. By paired random allocation, one of the patients was recommended mistletoe therapy by the attending physician. In 2 non-randomized matched-pair studies, cervical cancer patients without (102) and with (66) metastases, who already received mistletoe therapy, were matched with control patients without Iscador therapy. Results: For survival, the non-randomized studies showed significant effects in favor of Iscador therapy: hazard ratio (HR) estimate and 95% confidence interval (CI): 0.23 (0.14–0.39) and 0.37 (0.17–0.80), respectively. An effect of long-term Iscador therapy on tumor progression was not seen. Psychosomatic self-regulation in the Iscador group improved significantly within 12 months compared with the control group in the randomized as well as in 1 non-randomized study (cervical cancer without metastases): estimate of the median difference and 95% CI: 0.70 (0.15–1.05) and 0.25 (0.15–0.35), respectively. Conclusion: Iscador may have the effect of prolonging overall survival of cervical cancer patients. In the short term, psychosomatic self-regulation increases more markedly under complementary Iscador therapy than under conventional therapy alone.

Schlüsselwörter
Gebärmutterhalskrebs · Metastasen · Überleben · Lebensqualität · Komplementär- und Alternativmedizin · Anthroposophische Medizin · Mistel · Iscador

Zusammenfassung

Ergebnisse: Beim Gesamtüberleben zeigten nur die nicht-randomisierten Studien ein signifikantes Resultat zugunsten der Iscador-Therapie: Schätzwert des Hazard Ratio (HR) und 95% Konfidenzintervall (CI): 0.23 (0.14–0.39) bzw. 0.37 (0.17–0.80). Ein Effekt einer Langzeitanwendung von Iscador auf die Tumorprogression konnte nicht festgestellt werden. Das Niveau der psychosomatischen Selbstregulation stieg in der Iscador-Gruppe nach 12 Monaten sowohl in der randomisierten als auch in einer nicht-randomisierten Studie (Gebärmutterhalskrebs ohne Fernmetastasen) signifikant gegenüber der Kontrollgruppe: Schätzwert der medianen Differenz mit 95% CI: 0.70 (0.15–1.05) bzw. 0.25 (0.15–0.35).

Introduction

In Europe, many women with gynecological cancer use complementary therapies. However, evidence of their efficacy on disease progression and survival is still controversial [1]. Among complementary therapies for cancer patients, the aqueous extracts of European mistletoe (Viscum album L.), developed on the basis of anthroposophic medicine, is the most frequently used medication, particularly in the German speaking countries [2]. The 14 prospective controlled studies, published before the end of 2002, with the mistletoe extract Iscador® (Weleda, Schwäbisch Gmünd, Germany) show positive trends (n = 7) or significant results (n = 7) in favor of Iscador [3, 4]. The only 2 published prospective controlled studies concerning the treatment of cervical cancer with mistletoe extracts, particularly Iscador, are from the 1960s [5–7]. One of them [5, 6] shows a significant effect in favor of Iscador treatment, the other only a trend.

This paper reports on 3 new data sets concerning long-term therapy with the mistletoe preparation Iscador: 1 randomized matched-pair study with cervical cancer patients with distant metastases (19 pairs) and 2 non-randomized matched-pair studies with cervical cancer patients with (66 pairs) and without distant metastases (102 pairs). The 2 special design features of these cohort studies are the long-term follow-up and the integration of a prospective controlled cohort study with a randomized trial [8, 11]. Both the non-randomized studies and the randomized study rely on matching pairs of patients according to important prognostic factors: firstly, at the beginning of the study, available mistletoe-treated patients were matched with control patients, and for every new patient an additional control patient was found in the data base; secondly, within the same cohort of control patients (but without intersection with the group of already ‘used’ controls), matched pairs were built and, after randomization, mistletoe therapy was suggested to 1 of the patients of each pair. This design allows to compare the results of randomized and non-randomized matched-pair studies. The better internal validity of the randomized studies (given comparable results) is enhanced by the better generalizability of non-randomized studies [9, 10].

Patients and Methods

Only a brief description of the study design and matching methods is given, as their structure matches that of earlier studies. For further information we refer to [8, 11–13] as well as the supplementary materials, including background, tables and figures, at www.karger.com/doi/10.1159/000102956.

Study Objectives

The primary question was: Compared to standard conventional treatment alone, does long-term Iscador therapy in addition to conventional oncological treatment influence survival in patients with different stages of primary cervical cancer? Secondary questions included: Does long-term Iscador therapy in addition to conventional oncological treatment delay the time to recurrence and lymphatic or distant metastases in patients with primary cervical cancer compared to standard treatment alone? Does Iscador therapy in addition to conventional oncological treatment improve psychosomatic self-regulation in patients with cervical cancer compared to standard treatment alone?

Study Design

All 3 studies presented here were controlled cohort studies which have overall been prospective by design, i.e. starting in 1973, cervical cancer patients were recruited, assessed, matched according to pre-specified relevant prognostic factors and followed up for the duration of their life. The only intended difference between matched pairs was the presence or absence of therapy with the mistletoe preparation Iscador. The question whether Iscador is a relevant prognostic factor for cancer progression and survival as well as self-regulation was formulated right in the beginning of these studies in 1973.

There was no written study protocol and no initial sample size calculation since all 3 studies started in 1973 before the mandatory requirements of Good Clinical Practice were issued. Nonetheless, the structure of the initial and follow-up data assessments, the parameters to measure (self-regulation), the data to retrieve (medical parameters) and the matching criteria were specified prior to the start of all 3 studies.

Patients

Only patients with sufficiently complete medical records who were not participating in any other clinical trial were included in the studies. Each patient of the control and the therapy group received a form of conventional oncological treatment, including surgery, chemotherapy, radiotherapy and hormone therapy. As the matching process included the year of first diagnosis as a mandatory criterion, it was assured that matched patients received their first diagnosis and baseline treatment at similar times, making it very unlikely that different diagnostic procedures or modes of conventional therapy due to scientific progress were used between matched pairs. Consent to participate in the study was assumed after comprehensive information about the study objectives and the study design and explicit expression of each patient’s willingness to participate. There was no written documentation of this process, because at that time, there was no mandatory requirement for an ethics committee deeming the studies as adequate.

Initial Data Assessment

Personal data were supplied by the patients themselves or by their relatives. Medical data were supplied by the attending physicians or retrieved from clinical data records. Data were collected during structured personal interviews with standardized checklists and later recorded on cards in the patients’ files. There is no electronic data base for these raw data. In most cases, initial data were assessed within 3 years of the first diagnosis of primary cervical cancer. The zero point for all time-to-event data is the year of first diagnosis. The medical data were then checked and complemented through personal contact with the attending physician. Quality of life was assessed by the level of psychosomatic self-regulation using a questionnaire with 16 items [14–17, 21]. Self-regulation was used in our studies as a prognostic factor, and in 2 studies also as an endpoint where it was measured twice. In the former case, self-regulation indicates the status of autonomy at the beginning of the study, and in the latter case, it reveals how this status changed in 12 months in the course of various therapies [14, 15].

Observed Therapy and Intervention

In the non-randomized studies, the investigators did not interfere with the treatment decisions (Iscador therapy or not) of the patients or the attending physicians, but only observed the applied treatment. In the randomized matched-pair study, 1 partner of each pair was allocated to the proposal of Iscador treatment. In all 3 studies, Iscador therapy was not administered by study physicians but by a physician chosen by the patients themselves. The complementary therapy with Iscador that was applied in...
these studies in addition to conventional oncological treatments is an aqueous extract of the European mistletoe (V. album L.) that was first used for cancer therapy in 1918 by Rudolf Steiner and Ita Wegman on the basis of anthroposophy [22]. The pharmacological and toxicological properties of mistletoe extracts are documented in various publications on preclinical studies and immunological and anti-cancer effects in vitro and in vivo [2, 23–26]. The pharmaceutical properties of Iscador have essentially not been altered during the studies reported here. Iscador is generally administrated subcutaneously 2–3 times a week. There are different doses, different sorts of Iscador depending on the host tree, and different application schemes [24, 27]. Yet, to keep the studies as simple as possible, only the mere fact of Iscador therapy and its duration in months was documented. There is no information concerning doses, dose variations, therapy breaks, host trees, etc.

Matching Process for the 2 Prospective Non-Randomized Studies
The basis for building matched pairs for the non-randomized prospective studies was the group of cervical cancer patients with or without distant metastases at the time of first diagnosis already receiving Iscador therapy (table 1). The difference between the year of first diagnosis, which coincides with the year of first operation, and the year of initial data assessment was in most cases ≤ 3 years (data not shown). As the patients were consecutively recruited into the data pool from 1973 to 1998 (fig. 1, www.karger.com/doi/10.1159/000102956) and met all inclusion criteria, control patients were taken from the pool of already available patients from the data files with no mistletoe therapy and within the same data source. The matching process was performed within 12 months of a patient with Iscador therapy entering the study and the initial data assessment being completed. For the purpose of matching, it was checked whether a respective control patient was still alive, willing to participate in a controlled cohort study, and what kind of therapies she had received since the last contact. If no matching partner could be found, the Iscador patient in question was excluded. Every control patient participated only once in all mistletoe studies and never in different studies. Control patients were not excluded if they received mistletoe treatments during follow-up.

The matching criteria included the following broad categories (table 2): tumor stage and grading at first diagnosis, year of first diagnosis of cervical cancer with or without local recurrence or lymphatic or distant metastases (≤ 3 years; data not shown), age at first diagnosis (≤ 3 years), and type and combination of conventional therapies. In order not to lose too many patients, deviations in matching criteria were allowed in up to 2 criteria in both data sets (table 1), except for deviations in the year of first diagnosis. If more than 1 control patient was available, the pair with the smallest age difference was included in the study. A patient group with pairs with ‘strict matching’ is a subgroup of all matched pairs of patients that meet all matching criteria. A patient group with a ‘balanced set’ is a subgroup of all matched pairs of patients, out of which pairs with prognostic factors in favor of patients with Iscador therapy were eliminated. The latter lie in between the full data set and the set with strict matching.

Outcome Parameters
The primary end-time parameter was overall survival, i.e. the time from the first diagnosis to death for any reason (except certified non-tumor-related accidents and suicides). Secondary outcome parameters were tumor progression, i.e. time from first diagnosis to local recurrence, lymphatic metastases or distant metastases and self-regulation at the second assessment 12 months after the initial data assessment.

Follow-Up Patients were investigated by a team of scientific researchers of the Institute of Preventive Medicine (Heidelberg, Germany). Up to 1998, the team conducted standardized telephone interviews or home visits to make structured interviews at intervals of 1 to several months using predetermined case report forms in each case. Patients were asked about their well-being, disease progression, other diseases, continuation of conventional treatment, continuation of complementary therapy – particularly with Iscador if applicable – and the start of new therapies. To simplify matters, both the basic and any further therapies were recorded in broad categories only (tables 2, 4). Concerning further tumor events (recurrence, lymphatic metastases, distant metastases, death), only the year of occurrence was recorded. Matched patients in the randomized studies were always contacted within the same week or the 2 successive weeks. If necessary for precision and validity of the medical follow-up data, the at
Long-Term Therapy for Cervical Cancer with Iscador®

Results

Data Sets and Patient Characteristics

Randomized Matched-Pair Study: CervixMetRand

This included $2 \times 19$ patients with primary cervical cancer with distant metastases (tables 3, 4). The initial data assessment was performed between 1973 and 1984. Out of the available 329 primary cervical cancer patients with distant metastases that did not receive mistletoe therapy, 19 randomized matched pairs could be formed. By the time of the final assessment in 2002, all patients had died. No pair had to be excluded. The matching was almost perfect in all variables including stage (table 4).

Non-Randomized Matched-Pair study: Cervix

This included $2 \times 102$ primary cervical cancer patients of all stages with no distant metastases (tables 1, 2). The initial data assessment was performed between 1973 and 1998. Out of the available 109 primary cervical cancer patients with no distant metastases that already received mistletoe therapy, 106 non-randomized matched pairs could be formed using the pool of 504 patients not receiving mistletoe therapy (table 1). 102 matched pairs entered into the final analysis after the exclusion of 4 pairs (table 1). By the time of the final assessment in 2002, all patients had died. For details concerning differences in patient characteristics and the matching process for Cervix and CervixMet, see the supplementary materials at www.karger.com/doi/10.1159/000102956.

The data set CERVIX combines the data sets Cervix and CervixMet into 1 data set with 168 non-randomized matched pairs. The combination of the balanced sets includes 154 pairs, and the combination of the sets with strict matching includes 118 pairs (table 5).

Overall Survival

Overall survival was analyzed for all 3 data sets in several ways (table 5). The results indicate a prolonging effect of Iscador therapy on survival. In the randomized study CervixMet-Rand, the effect estimate with the Cox model shows a trend in favor of Iscador therapy (hazard ratio (HR) estimate and 95% confidence interval (CI): 0.46 (0.18–1.21), p = 0.12; proportional hazard assumption moderately fulfilled). Since there are no censored survival times, this is supported by the effect estimate (median difference of survival time) according to the Wilcoxon paired sample test: 0.44 (−0.17–1.00), p = 0.16.

The results for the non-randomized studies Cervix and CervixMet are significant for all individual studies, their subsets, and the adjusted and unadjusted estimates, and for the combined set CERVIX the results are even highly significant in all analyses (table 5). The Cox models are all adequate and there are no significant interactions. On average, the possible gain in survival in the Iscador group is more than half a year. The Kaplan-Meier survival curve for CervixRand is shown in figure 2 (www.karger.com/doi/10.1159/000102956). The adjusted survival curves for Cervix, CervixMet and CERVIX according to the models with the adjusted variables indicated in table 5 are shown in figure 3.

Time to Recurrences, Lymphatic Metastases or Distant Metastases

For Cervix (102 non-randomized matched pairs), the time to local recurrence, lymphatic metastases or distant metastases was recorded independently. 5 different analyses were performed (table 6, fig. 4, www.karger.com/doi/10.1159/000102956). Looking at the results, only local recurrences and distant metastases occurred, with the time to event not differing much between the 2 groups: taking into account censored event times, no difference was significant. However, taking all events, including death, together, both models showed a highly significant effect in favor of Iscador therapy: HR estimate for ordered events and 95% CI: 0.32 (0.22–0.48).
Self-Regulation

Psychosomatic self-regulation was assessed twice for both CervixMetRand and Cervix. The second assessment was 12 months after the initial one. For CervixMetRand, the effect estimate (median difference and 95% CI) was 0.70 (0.15–1.05) with \( p = 0.014 \). For Cervix, the Wilcoxon paired sample test was applied to the full set, the balanced set and the set with strict matching; the effect estimate is the same in all cases: 0.25 (0.15–0.35) with \( p < 0.0005 \). Both studies show significant improvements. Hence, Iscador therapy may help improve the clinical well-being of cervical cancer patients.

Adverse Events

The registration of adverse events of either Iscador therapy or conventional treatment was not part of the study design. Hence, no information on such events is available.

Discussion

The design and analysis features of these studies, the general limitations (bias) of our approach, and the properties of the evaluation of psychosomatic self-regulation have already been discussed in [8, 11] and will not be repeated here. The exact onset and duration of Iscador therapy did not enter into the analysis. Patients that had Iscador therapy only for a short time died early. There were no patients that stopped Iscador therapy after study initiation for other reasons than death or lost-to-follow-up (1 patient in Cervix).

For overall survival, CervixMetRand (19 pairs) shows a positive trend in favor of long-term complementary Iscador therapy as compared to conventional treatment alone. However, the improvement of psychosomatic self-regulation after 12 months is highly relevant and significant in favor of the Iscador group. Since matching was accomplished within 12 months of the initial data assessment, misclassification due to shifting criteria is unlikely. Selection bias is neutralized by the randomization process. Performance bias is not a problem, since the main co-interventions were recorded (data not shown). In addition, it is plausible to assume that the control patients used additional (unconventional and unrecorded) therapies more often, since no such treatment was offered to them by means of study participation; generally speaking, this works in favor of the control group. Detection bias is a minor problem, since in these studies, objective criteria of clinical diagnosis and survival were used; there is no reason to assume that either group was watched more closely for the incidence of tumor-related events. Attrition bias cannot happen, since no cases were lost cases in the study CervixMetRand.

In all, overall survival in the 2 non-randomized studies is significant in favor of Iscador therapy in all cases of analysis, particularly with strong effects in the study Cervix with patients having no metastases. The results concerning the time to event of local recurrence and distant metastases (there were no events of lymphatic metastases) are not convincing in favor of any therapy group. One needs to keep in mind that there were only 6 or less events per group. However, the improvement of self-regulation after 12 months is significant in favor of the long-term complementary Iscador therapy vs. conventional treatment alone in both studies.

Paired matching was used to reduce selection bias in the non-randomized studies for several known prognostic factors. However, to recruit a relevant number of patients, matching could not be performed without some exceptions. In order to deal with the biases due to lose matching with up to 2 deviations from strict matching, several analytic approaches were applied as a kind of sensitivity analysis: within non-adjusted analyses, balanced subsets and sets with strict matching were formed and analyzed separately to compare results. In addition, Cox proportional hazards models were built with and without adjustments of factors other than therapy (including
interactions of the first kind, if significant). In an additional sensitivity analysis, the results of all cervical cancer patients with distant metastases \( n = 2 \times 69 \) were compared with the results of the full set CervixMet \( n = 2 \times 66 \), and no relevant differences were found (data not shown). Such an analysis could not be performed for the full set Cervix \( n = 2 \times 106 \) since all 4 pairs that were excluded were also excluded from the data base and hence not followed up. Concerning overall survival, the unadjusted analyses show comparable results for the different subsets, proving that the original sets were well balanced, at least with respect to the prognostic factors used in the matching process. This is supported by the fact that the results of the Cox proportional hazards model do not differ very much between the adjusted and the unadjusted analysis. Concerning the time to recurrence and distant metastases, the different approaches taking into account censored event times yield similar results. Since most of the event times are censored, the Wilcoxon paired sample test cannot give reliable results, in contrast to the stratified log-rank test. Still, several other biases might limit the study results. For the same reason as in the case of the randomized study CervixRand, biases due to lack of accuracy and misclassification are of minor importance. The same applies to performance and detection bias. The most important sources of bias for non-randomized studies are selection and confounding [36]. More specifically, residual bias might stem from i) non-perfect matching, ii) non-matched prognostic factors, and iii) not measured (un)known prognostic factors. The first case has already been dealt with. The second and third cases are more serious. According to the study design, several important medical prognostic factors were either not recorded throughout all cases, or not recorded at all (i.e. steroid receptor, histopathological type and histopathological grading). In addition, other factors were not deemed relevant for the study objectives at the outset of the studies in 1973 and hence are not available for analysis (i.e. exact dates of first diagnosis, operation, initial and follow-up data assessments and matching; socioeconomic status; social support; spirituality). The source of recruitment and the hospital were dropped for reasons of anonymity. This leaves the case of unknown factors open to speculation. Attrition bias is a minor problem, since with the dropout of any study patient her matching partner was excluded as well, and hence, the balance of the groups was not severely affected. There is no evidence that the reason for dropout is related to the outcome.

The (internal) validity of the results is, first of all, limited by selection bias and confounding as discussed above. And one has to bear in mind that due to the fact that these studies were not blind it is impossible to say whether any positive effects the patients may have experienced were due to the pharmacological effects of the mistletoe preparations or the psychological effects of hope and expectation associated with the treatment. Further limitations of validity might arise from the fact that there was no written protocol and hence no pre-specified formulation of statistical hypotheses; the sample size was small and there were neither sample-size calculations in advance nor adjustments for multiple testing. Still, in many cases the estimated effects are very strong and thus not affected by these limitations. As in the case of the randomized study, the generalizability (external validity) of the non-randomized studies might be limited by the fact that the inclusion and exclusion criteria were neither very precise nor always explicitly formulated in advance. Furthermore, apart from the matching criteria, there were no explicit procedures for building pairs. It was simply looking for the best matching partner. In the case of deviations from the main matching criteria, there was no rule for how to proceed. In these studies, there might have been a preference for patients with good prognosis, as patients from either group who died shortly after the diagnoses could not enter into the study.

Concerning the short-term improvement of psychosomatic self-regulation in Cervix, estimated by the median of the pairwise differences in self-regulation between the second and first evaluation, the analyses of the original set and the subsets show a highly significant improvement. However, the estimate of the median of improvement is well below 0.5; given the high initial values in both groups, these minor improvements of the Iscador group vs. the control group may still be clinically relevant [17].

Consistency and Generalizability

The baseline values of CervixMetRand and CervixMet are comparable and so are the results. That is, although not in all cases significant, the results of CervixMetRand are consistent with those of CervixMet: they point in the same direction. Together, both studies gain from each other. The first has better internal validity and the latter has better generalizability. There are 2 prospective controlled studies concerning the treatment of cervical cancer with Iscador [5–7]. References for case series can be found in [2, 4]. Only one of these controlled studies [5, 6] received fairly good marks about overall study quality from 2 different reviews [3, 37]. The other one [7] is of low quality [3, 37]: it does not report sufficient data and no statistical analysis for judging the validity of the result. The first study with 81 long-term (up to 5 years) Iscador-treated patients and 709 controls reports a significant result concerning 5-year survival \( p = 0.015 \). The selection process is not specified sufficiently so that the comparability of the study groups is not fully guaranteed (no explicit protection against selection bias). However, the overall results of this study compares well with the results of our study Cervix with 102 matched pairs: both studies are significant in favor of Iscador therapy, and the patients were of approximately the same age and included the same stages (however, 9 pairs of patients in Cervix had stage IVA).

2 recently published non-randomized controlled studies show a tendency for improvement of overall quality of life and a reduction of side effects of chemotherapy in patients with gyne-
cological cancers treated with Iscador in addition to conven-
tional therapy vs. patients receiving conventional therapy
alone [38, 39]. In-patient therapy at an anthroposophical hos-
pital might further improve quality of life [44].

Tolerability and Safety
A documentation of unintended adverse drug reactions to Is-
cador therapy was not part of the design of these studies. How-
ever, there is no evidence for severe adverse effects that
can be plausibly related with this therapy [2, 40, 46–48]. This
has also been supported by more recent data on the tolerabil-
ity and safety of complementary therapy with Iscador [41, 42].
This is also true for anthroposophic treatments in general [45].
In addition, apart from its effects on the prolongation of sur-
vival, mistletoe therapy with Iscador seems to reduce the side
effects of conventional chemotherapy [38, 39, 41, 43], i.e. help
patients to live better through the ill-effects of chemotherapy.

Conclusion
The consistency of the results across the randomized and the
non-randomized studies as well as across different types of
analyses give some evidence that the long-term therapy with
Iscador might have clinically relevant therapeutic effects on
overall survival in these studies for cervical cancer patients.
In the short term, psychosomatic self-regulation as a measure of
autonomous coping with the disease, improves significantly
more under Iscador therapy compared to conventional ther-
apy alone. Overall, Iscador therapy may prolong survival and
improve the well-being of cervical cancer patients to a clinically
relevant extent.

Supplemental Files
For further information about Background, Institutional Setting, Sources
of Funding, Contributors, Acknowledgements as well as the following fig-
ures and tables please refer to www.karger.com/doi/10.1159/000102956.

Fig. 1. Flow chart for the pool of sources of study patients with cervical
cancer for randomized and non-randomized matched-pair studies

Fig. 2. Cervix: Kaplan-Meier survival curves for the full set show-
ing the two groups with and without Iscador.

Fig. 4. Cervix: Adjusted time to event curves for time to local recur-
rences showing the two groups with and without Iscador, based on the
model in table 6 (type of analysis: III).

Table 1. Flow chart of primary cervical cancer patients from the non-
randomized matched-pairs studies Cervix and CervixMet
Table 2. Patient characteristics (matching variables and other variables
in the non-randomized matched-pair studies Cervix and CervixMet
Table 3. Flow chart of primary cervical cancer patients with distant
metastases from the randomized matched-pair study CervixMetRand
Table 4. Patient characteristics (matching variables and other variables
in the randomized matched-pair study CervixMetRand
Table 5. Overall survival for the data sets with non-randomized matched
pairs: Cervix and CervixMet and their combination into CERVIX
Table 6. Cervix: Number of events and time to the event of local recur-
rences, lymphatic metastases and distant metastases.