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OUTCOMES BASED ON HISTOPATHOLOGIC RESPONSE TO PRE-OPERATIVE CHEMOTHERAPY IN CHILDREN WITH BILATERAL WILMS TUMOR-A PROSPECTIVE STUDY (COG AREN0534)

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ABSTRACT

Background: An objective of AREN0534 was to improve survival for bilateral Wilms tumor (BWT) patients using preoperative chemotherapy of limited duration and tailoring postoperative therapy based on histopathologic response. We report outcomes based on postoperative histopathologic response.

Methods: BWT patients were treated with vincristine (V), dactinomycin (A), and doxorubicin (D) for 6 or 12 weeks followed by surgery. Postoperative therapy was prescribed based on the highest risk tumor according to SIOP classification and the Children's Oncology Group (COG) staging system.

Results: Analyses were performed on data from 180 evaluable children. The 4-year event-free survival (EFS) and overall survival (OS) were 81% (95% CI: 74%-87%) and 95% (95% CI: 91%-99%), respectively. Seven patients with completely necrotic tumors had a 4-year EFS of 100%. Of 118 patients with intermediate-risk histopathology, the 4-year EFS was 82% (95% CI: 74%-90%) and OS: 97% (95% CI: 94%-100%). Fourteen patients with blastemal type had a 4-year EFS of 79% (95% CI: 56%-100%) and OS: 93% (79%-100%). Eighteen patients with diffuse anaplasia had a 4-year EFS of 61% (95% CI: 35%-88%) and OS of 72% (95% CI: 47%-97%); 4-year EFS of 7 patients with focal anaplasia was 71% (95% CI: 38%-100%) and OS: 100%. There was no difference in outcome with different histopathologic subtypes within the intermediate risk group (p=0.54).

Conclusion: A risk-adapted treatment approach for BWT results in excellent outcomes. This approach was not successful in improving the outcome in patients with diffuse anaplasia.

Introduction: Children with Bilateral Wilms Tumor (BWT) account for 5% of all patients with Wilms tumor. Historically, chemotherapy prior to definitive surgery was the standard of care to preserve adequate number of normal functioning renal units.[1-3] While this continues to be an important goal, the outcome of children with bilateral Wilms tumors from the National Wilms Tumor Study (NWTS-5) was suboptimal with a 4-year EFS and OS of 56 and 80.8%% respectively [4]

In NWTS-5 patients with BWT and favorable histology the relapse-free survival was 65%[5]. For focal anaplastic and diffuse anaplastic BWT, the four- year EFS estimates were 76% and 25%, respectively.[6] The reasons for this suboptimal outcome were likely due to 1) inadequate staging 2) delay in definitive surgery and therefore delay in the assessment of final histopathology, and 3) prolonged chemotherapy prior to definitive surgery exposing patients to both acute and long-term toxicities

but with no effect on renal preservation or overall treatment outcome.[7-10] Children's Oncology Group (COG) launched the first prospective multi-institutional study of children with bilateral Wilms tumors to address the factors mentioned above and improve the outcome of these patients.[11] Children with bilateral renal masses with typical clinical and radiologic features of BWT could start therapy without a diagnostic biopsy. In patients who did not meet these criteria or were older than 10 years of age, a diagnostic biopsy was strongly encouraged. All received preoperative chemotherapy with three drugs for 6 or 12 weeks depending on tumor response and the feasibility of nephron sparing definitive surgery (see Patients and Methods). The subsequent treatment was based on risk assignment which took into account the histopathologic response and stage. Particularly, when assigning treatment postoperatively we decided to use the lessons learned from the SIOP experience especially with regard to "necrotic type" and "blastemal type". The initial report describing the excellent outcomes and the advantages of this approach was recently published.[11] We report outcomes in patients stratified in risk groups based on histopathologic response to preoperative chemotherapy.

Patients and Methods: COG study AREN0534 (2009 - 2015), "Treatment for Patients with Bilateral, Multi-centric, or Bilaterally-Predisposed Unilateral Wilms Tumor" had three arms: one for treatment of patients with BWT, one for patients with unilateral tumors at high-risk for metachronous disease or multi-centric tumors, and one for patients with diffuse hyperplastic perilobar nephroblastomatosis (DHPLN) (see supplementary files).

*Enrollment and Eligibility***:** Patients were enrolled after institutional review board or research ethics board approval and patient or guardian consent. Patients <30 years of age with synchronous bilateral renal masses 1 cm or greater on radiographic imaging were eligible. All patients received an initial risk assignment through the biology and classification study AREN03B2 with real-time central radiology review (and pathology review, if a biopsy was performed). A diagnostic biopsy was not required but patients with a diagnostic biopsy or definitive surgery at diagnosis were still eligible. Enrollment

was required within 14 days of diagnosis or 7 days after starting therapy. Patients with an isolated lesion less than 1 cm in the contralateral kidney could be treated by nephrectomy with post-operative therapy based on the pathologic findings. These patients were eligible to enroll on another therapeutic study.

Staging: Patients with BWT were assigned both a local stage and an overall disease stage. The final local stage was based on the abdominal tumor spread, whereas the disease stage accounted for the presence of distant metastatic disease..[12] In the setting of bilateral renal tumors, the highest local stage is III, stage IV represents liver involvement or extra-abdominal metastatic disease and stage V is assigned to patients with bilateral disease regardless of disease extent.[12]

Treatment: Pre-operative treatment was to begin within 14 days of a surgical procedure (for those that had a procedure) or radiological diagnosis of BWT. The overall strategy of the study was to administer pre-operative chemotherapy with the goal to perform bilateral partial nephrectomies. Initial induction therapy included vincristine, dactinomycin and doxorubicin (regimen VAD) for two cycles at three weeks per cycle (dosing and regimen in supplemental files). After six weeks, cross-sectional imaging was performed and a tumor response was assigned for each kidney (see response criteria below). If it was deemed feasible by the local institution to perform bilateral partial nephrectomies, surgery was to be undertaken. If the tumors achieved a partial response (PR) but were not yet amenable to bilateral partial nephrectomy, chemotherapy was continued for another two cycles. At week 6 if tumors in either kidney did not achieve a PR, bilateral open renal biopsies were recommended to assess the histologic reason for non-responsiveness. After four cycles of VAD (12 weeks), repeat cross sectional imaging was performed and definitive surgery was required by protocol.

Chemotherapy: Adjuvant therapy was based on local and overall tumor stage and histologic response after either six or twelve weeks of chemotherapy (see

supplementary files). The final risk stratification was based on both post-surgery staging as well as the post-chemotherapy pathology classification based on previous SIOP experience which showed that histologic type with complete necrosis indicated an excellent prognosis while blastemal type indicated high risk for progression.[12] This is the first experience within COG for a prospective study which required pre-operative chemotherapy and we wanted to use treatment regimens and staging COG investigators are familiar with while acknowledging prognostic significance of post-operative histopathologic types from the SIOP experience. Favorable histology Wilms tumor (FHWT) were sub classified based on the percentage of tumor necrosis and the percentage of viable components of the blastemal, epithelial or stromal types in the tumor following pre-operative chemotherapy. The histologic risk category was determined by the degree of necrosis, and by the component comprising greater than 65% of the viable tumor (blastemal, epithelial, stromal, or in the absence of predominance, mixed). Completely necrotic tumor (allowing for residual viable nephrogenic rest elements) was classified as low risk. FHWT with >67% necrosis (considered regressive by SIOP) were classified as intermediate risk (regardless of histologic subtype). Also within the intermediate risk category were FHWT with greater than 35% viable elements that showed >67% stromal or epithelial histology, or that showed no predominant pattern (mixed). FHWT with >35% viable tumor of which >67% was blastema was considered to be high risk for which treatment was intensified using regimen I. Tumors with focal and diffuse anaplasia were treated according to current treatment regimens for their respective histology and stage in unilateral tumors (see supplementary files). Treatment was assigned based on the highest risk WT in each patient. For example, if one kidney had a completely necrotic tumor and the other kidney had a tumor with mixed type then the patient was assigned to the intermediate risk category and not low risk category. If there was diffuse anaplasia in one and the other had mixed or epithelial then the patient was assigned to the diffuse anaplasia regimen. The chemotherapy regimens have been used in prior COG studies, however in the recent studies the regimens changed with respect to mg/kg versus mg/m^2 dosing (VAD, EE4A, DD4A, I and UH-1/revised UH-1) (see supplemental files).

Patients with diffuse anaplasia were on UH-1 at the beginning of this study and then switched to revised UH-1 when AREN0321 was amended (11/23/2009). Assignment of stage was based on the kidney with the highest stage. For example, if one kidney was stage I and the other stage III, the latter was considered in risk assignment.

Radiation therapy: For favorable histology tumors that were classified as abdominal stage III, flank radiotherapy with 10.8 Gy was utilized (19.8 Gy for ≥16 years old). A difference from other COG studies for unilateral Wilms tumor was that although needle or open biopsies prior to chemotherapy were considered as a criterion for stage III, these patients were not mandated to receive flank radiation therapy if there were no other reasons for stage III designation. Tumor necrosis present at the margin or within lymph nodes was considered local stage 3; tumor necrosis without viable tumor outside of the kidney but completely excised was considered stage 1. Completely necrotic tumors were assigned to receive irradiation in case of stage III, which is different from practice in SIOP. The details of radiation therapy are as described in Ehrlich et al. and are included in supplementary files page 6.[11]

Response: Response was based on the Response Evaluation Criteria in Solid Tumor (RECIST 1.1) modified to include 3 lesions per kidney. Target lesions were defined as lesions greater than 10mm within the kidney. If multiple target lesions were present at least 3 of them were described. Each kidney was assessed separately. PR was defined as at least a 30% decrease in the sum of the diameters of target lesions, progressive disease (PD) was defined as at least a 20% increase in the sum of the diameters of target lesions and stable disease (SD) as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Statistics

Survival time was calculated from the date of study entry to the time of event or last follow-up. Tumor progression, relapse, occurrence of second malignancy, or death due to any cause were considered for event free survival (EFS). Overall survival (OS) was

measured from the date of study entry to death from any cause. Patients still alive at the time of data cut-off (9/30/2018) were censored at the date of the last observation. Survival probability was calculated by the Kaplan-Meier method, with the 95% confidence intervals (CI) computed using the Peto-Peto method.[13] Survival curves were compared by the Log-Rank test. Categorical variables were reported as counts and percentages and compared using Fisher's Exact test. All data analyses were performed using R version 4.0.1.

Results:

Patients:

The study enrolled 201 patients (Fig1). All children were less than 10 years of age. The numbers differ slightly from Ehrlich et al. for the reasons as listed in the Consort Diagram. Six were ineligible, and 15 were unevaluable as explained in the Consort diagram. Biopsies were performed in 12 patients at diagnosis. Of the three patients with biopsies of both kidneys, one had a fine needle biopsy and two had open biopsies. Of the 9 patients who had biopsies of one kidney, 7 had open biopsies and 2 tru-cut needle biopsies. Of the three patients with biopsies of both kidneys, two had FHWT in both kidneys and one had "Nephroblastic lesion, indeterminate between rest and Wilms Tumor" in one kidney (due to insufficient material) and FHWT in the other. In the 9 patients with biopsies of one kidney, 6 had FHWT and 3 had "Nephroblastic lesion, indeterminate between rest and Wilms Tumor".
At week 6 biopsies were performed in 23 patients, 16 in both kidneys and 7 in one kidney. Of the 16, open biopsies were performed in 13, one each with tru-cut and fine needle and one with fine needle in one kidney and open biopsy in the other. All 7 patients who had only one kidney biopsied had an open biopsy.

Of the 180 patients with evaluable post-surgery pathology determined by central review, 19 were considered low risk: 7 with complete necrosis and rests only in 12. There were 122 patients with intermediate risk histopathology: 78 mixed, 21 stromal, 18 epithelial,

and 1 predominantly necrotic (regressive). There were 4 patients who did not receive definitive surgery either at week 6 or week 12 but did have centrally reviewed pathology when they finally had surgery performed. These 4 patients were not included in the survival analyses although the pathology was reviewed. All 4 of these patients had intermediate risk histopathology. There were 14 patients with blastemal type histopathology. Of the 25 patients with anaplasia, 18 were diffuse and 7 were focal.

Response:

Definitive surgery was performed at 6 weeks in 47 patients and at 12 weeks in 129 patients. As shown in Table 1, of the 21 with stromal differentiated tumors 13 were stable and 5 had progressive disease after preoperative chemotherapy. However, the 4-year overall survival was 100%. The majority of patients with other histologies achieved partial responses (PR) to preoperative chemotherapy (Table 1). There were no differences in survival based on responses or stages within each histologic category (Table 2, Fig. 2). But the numbers in each of these categories are low and therefore definite conclusions cannot be drawn.

Outcome: The 4-year event-free survival (EFS) of all 176 patients was 80.6% (95% CI: 73.9%-87.3%) while the overall survival (OS) was 94.8% (95% CI 91.1%-98.5%) (Fig. 3). The 4-year EFS and OS for low, intermediate, and high-risk patients were 94.7% (95% CI 82.9%-100%) and 100%, 82.0% (95% CI 74.3%-90.3%) and 97.4% (95% CI 94.1%-100%), 78.6% (95% CI 56.0%-100%) and 92.9% (95% CI 78.8%-100%) respectively (Fig. 4). Of the18 patients with diffuse anaplasia, the 4-year EFS and OS were 61.1% (95% CI 34.7%-87.5%) and 71.8% (95% CI 46.9%-96.7%) and those with focal anaplasia 71.4% (95% CI 38.0%-100%) and 100%, respectively. Three patients had stage IV with diffuse anaplasia and one of them died of disease. Among the patients with low-risk tumors, those with completely necrotic tumors had 100% 4-year EFS and OS (Fig. 5). Within the intermediate risk category, the EFS for the epithelial subtype was 77.8% (95% CI 53.8%-100%) compared to mixed 83.43 (95% CI 73.8%-93%) and stromal 85.21 (95% CI 68%-100%) p=0.54. Those with blastemal type

histology stage III had a 4-year EFS of 83.3% (95% CI 50.0%-100%). There were only 2 patients with stage IV with blastemal type histology.

Discussion: Synchronous BWT is observed in only about 5% of all children with Wilms tumors. There has not been a uniform approach to management of these tumors, given their rarity and the variations in their presentations (nephrogenic rests vs tumors). This study is the first prospective study for children with BWT which prescribed a more intensive initial therapy and definitive surgery after 6 or 12 weeks of chemotherapy. [11]

Preoperative chemotherapy without a biopsy has not been a standard practice in the clinical trials conducted by NWTSG and later the COG. Therefore, risk grouping based on postoperative histopathology was not previously incorporated into treatment assignment on prior studies. This study for BWT marks the first attempt within the COG to assign treatment based on postoperative histopathology. We pursued this approach as there were no established guidelines as to 1) how long preoperative chemotherapy should be given, 2) how tumor size response should guide timing of surgery (given that lack of response could represent a spectrum from differentiated tumors to anaplastic histology tumors) and, 3) the lack of prospective evidence that earlier definitive surgery and therapy stratified on postoperative histopathology improves outcomes in BWT[11]. Whilst postoperative histopathology risk stratification is a hallmark of SIOP trials, this study differs in the following ways: 1) this is a prospective study of BWT, 2) the preoperative therapy is uniformly intense with VAD of either 2 or 4 courses prior to surgery either at 6 or 12 weeks, 3) the pathology was reviewed centrally before assigning treatment and 4) postoperative clinical staging is based on COG staging guidelines while incorporating histopathology findings following preoperative chemotherapy (modified from SIOP experience). Risk assignment for treatment was based on both staging and post-operative histopathology. For the final postoperative assignment of treatment, we took the SIOP experience into account. We did assign patients with complete necrosis to low-risk and those with blastemal type histopathology to high risk categories to assign subsequent treatment.

One of the challenges of initiating chemotherapy without a prior tissue evaluation is the interpretation of histopathology and risk assignment following post-chemotherapy definitive surgery. Trials from SIOP have provided information about the histopathologic data and the outcomes based on these post-operative histopathologic assessments in children with unilateral Wilms tumors. Children with completely necrotic tumors, stromal predominant pathology, or epithelial predominant pathology have been described to have an excellent prognosis whereas those with blastemal type tumors have the worst prognosis.[14-18] Weirich et al. reported that recurrences were not seen in epithelial and stromal predominant and completely necrotic tumors, whereas 38% of blastemal type and 11% percent of mixed subtype recurred. Four-year recurrence-free survival was 61% and 89% for blastemal type and mixed subtype respectively.[15] Results of SIOP 93-01 again showed that blastemal type had an inferior 5-year event free survival of 82% compared to other histologic subtypes.[16] A report from SIOP-RTSG described the results of SIOP WT 2001 protocol trial in which patients with blastemal type following pre-operative chemotherapy were considered to be at high risk for recurrence and stage I was treated with the addition of doxorubicin to actinomycin D and vincristine and stages II and III blastemal type were treated with a more intensive regimen of doxorubicin, etoposide, cyclophosphamide and carboplatin.[14] This approach improved the 5–year EFS of stage I blastemal type (96% compared to 71% in SIOP 93-01; p=0.03) and stages II/III (77% vs 61%; p=0.05), though only stage I demonstrated a statistically significant difference in OS with the augmented treatment approach. Volume at surgery, age, stage, and treatment protocol appeared to be prognostic variables for EFS by multivariable Cox regression analysis.[14] As noted in SIOP data, response to preoperative therapy does not always predict outcome (Fig. 4)[15]. Eighteen of 21 patients with stromal differentiation in our study who had either stable or progressive disease still had an excellent outcome. A recent report also showed tumors with subtotally necrotic WTs (STN—WT) with >95% chemotherapy induced changes shared the same excellent prognosis as those with completely necrotic WT (CN—WT). In our study we did not further classify tumors into STN-WT.[17]

A report from SIOP-9 showed that there was a significant difference in the tumor response based on histopathologic subtypes. Stromal and epithelial types showed little change to preoperative chemotherapy whereas more than 50% of those with mixed, blastemal, and completely necrotic types were good responders with ≥40% reduction in volume .[15] In our study, the majority of patients with epithelial type also had partial responses. This could be due to moderately intensive preoperative chemotherapy with vincristine, dactinomycin and doxorubicin eliminating the non-epithelial components or eliciting responses in predominantly epithelial tumors.

In the recent report from COG on patients with stage III favorable histology *unilateral* Wilms tumor 116 out of 535 patients underwent delayed nephrectomy .[19] Of these 80 had specimens submitted for central pathology review. The 7 patients who had low-risk disease had 4-year EFS of 100%, 63 intermediate risk patients had a 4-year EFS of 90.5%, and 7 patients with blastemal type/high risk had a 4-year EFS of 28.6%. All of these patients were treated as stage III favorable histology and received the standard regimen of DD4A consisting of vincristine, dactinomycin, and doxorubicin and radiation therapy as indicated. In the present study 6 patients with stage III blastemal type histology had a 4-year EFS of 83%. The combination of preoperative therapy as prescribed in this study along with risk stratified regimen I with or without radiation therapy for stages II-IV blastemal type may have contributed to the improved outcome.

The AREN0534 data also suggest improved EFS in patients with BWT and diffuse anaplasia treated with Regimens UH-1/Revised UH-1 (4-year EFS of 61.1%, 95% CI 34.7%-87.5%) compared to Regimen I on NWTS-5 (4-year EFS of 25.1%, 95% CI 5.88%-51.0%).[6] This parallels the improved disease control observed with unilateral diffuse anaplastic WT, with more intensive treatment regimens .[20]

Information regarding 1q gain, LOH for 1p and 16q are not available for this study. Another limitation of this study is the lack of genomic studies which could have shed light on the development of these tumors and also a better understanding of the histologic types. Given the rarity of these tumors any prospective study is limited by the small sample size of the various histologic types

In conclusion, moderately intensive preoperative chemotherapy with early surgical intervention and appropriate treatment modification based on post-operative histopathology and clinical staging improved the outcome of patients with BWT compared to historical outcomes for children with BWT within COG.[11] Innovative approaches are required to improve the outcome for children with diffuse anaplasia.

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LEGEND

Table 1

Responses to pre-operative chemotherapy prior to definitive surgery at week 6 or 12. CR: Complete Response, NE: Not Evaluable, PD: Progressive Disease, PR: Partial Response, SD: Stable Disease

Table 2

Event-free survival (EFS) and Overall survival (OS) based on histopathology and staging following preoperative chemotherapy

Figure 1.

Consort diagram

Figure 2

A. Event-free survival (EFS) based on response to pre-operative chemotherapy
B. Overall survival (OS) based on response to pre-operative chemotherapy
CR: Complete Response, PD: Progressive Disease, PR: Partial Response, SD: Stable Disease

Figure 3.

Event-free survival (EFS) and overall survival (OS) of all 176 evaluable patients

Figure 4

A. Event-free survival (EFS) of patients with low, intermediate, and high risk tumors based on histopathology following pre-operative chemotherapy (high-risk represents blastemal type only and does not include tumors with anaplasia)

B. Overall survival (OS) of patients with low, intermediate, and high risk tumors based on histopathology following pre-operative chemotherapy (high-risk represents blastemal type only and does not include tumors with anaplasia)

Figure 5.

A. Event-free survival (EFS) of patients with tumors with complete necrosis and those with rests only

B. Overall survival of patients with rests only

Table 1

Responses to pre-operative therapy

Table 2

	Anaplasia	Blastemal	Complete Necrotic	Epithelial	Mixed	Stromal
CR	1	0	0	1	1	0
NE	1	0	0	1	2	0
PD	2	0	0	0	5	5
PR	9	12	6	13	43	3
SD	12	2	1	3	27	13
Total	25	14	7	18	78	21

12 patients who had rests only and 1 patient with predominantly necrotic tumor (regressive type) were not included in the table.

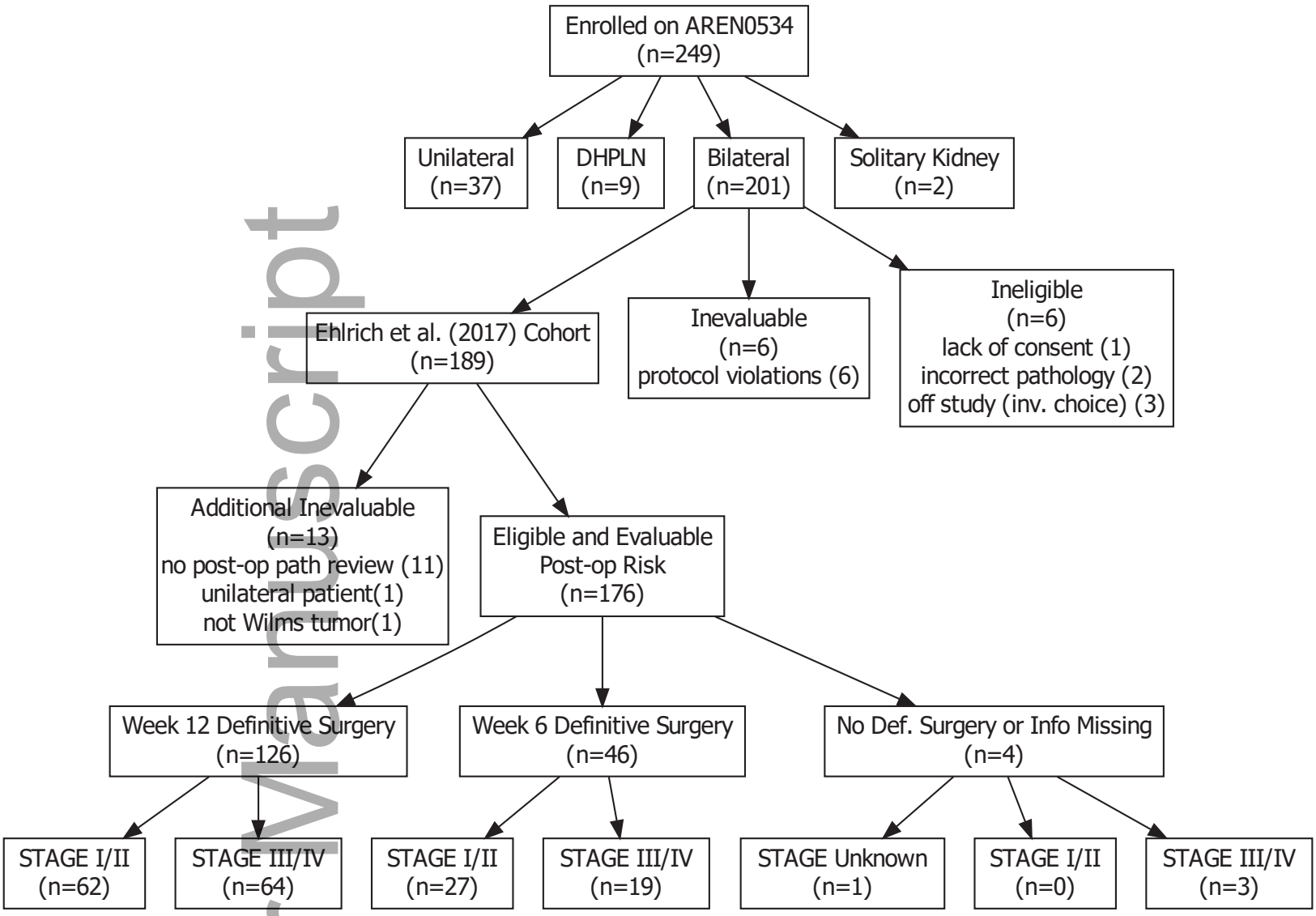
Event-free survival (EFS) and Overall survival (OS) based on histopathology and staging following preoperative chemotherapy

Histology*	Stage	n	4-year EFS (95% CI)	4-year OS (95% CI)
Blastemal	I	2	50% (0%-100%)	50% (0%-100%)
Blastemal	II	4	100%	100%
Blastemal	III	6	83.33% (50%-100%)	100%
Blastemal	IV	2	50% (0%-100%)	100%
Completely Necrotic	I	6	100%	100%
Completely Necrotic	II	0	NA	NA
Completely Necrotic	III	0	NA	NA
Completely Necrotic	IV	1	100%	100%

Histology*	Stage	n	4-year EFS (95% CI)	4-year OS (95% CI)
Epithelial	I	7	71.43% (38%-100%)	100%
Epithelial	II	3	100%	100%
Epithelial	III	6	83.33% (36.2%-100%)	100%
Epithelial	IV	2	50% (0%-100%)	100%
Mixed#	I	27	76.84% (60.2%-93.5%)	96.3% (88.9%-100%)
Mixed	II	12	91.67% (70.5%-100%)	100%
Mixed	III	29	89.66% (76.7%-100%)	96.55% (88.9%-100%)
Mixed	IV	9	77.78% (41.8%-100%)	88.89% (59.9%-100%)
Stromal	I	8	100%	100%
Stromal	II	2	50% (0%-100%)	100%
Stromal	III	10	78.75% (49.7%-100%)	100%
Stromal	IV	1	100%	100%

#One mixed type patient had an unknown stage and was not included.

*This table does not include 25 patients with anaplasia



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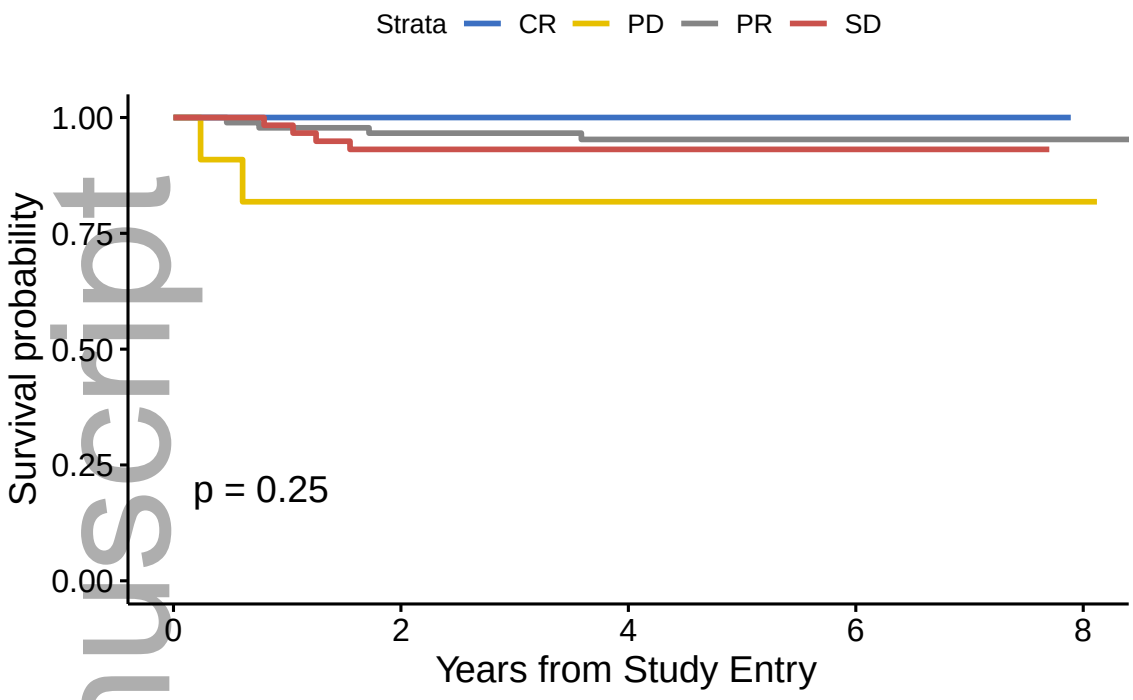
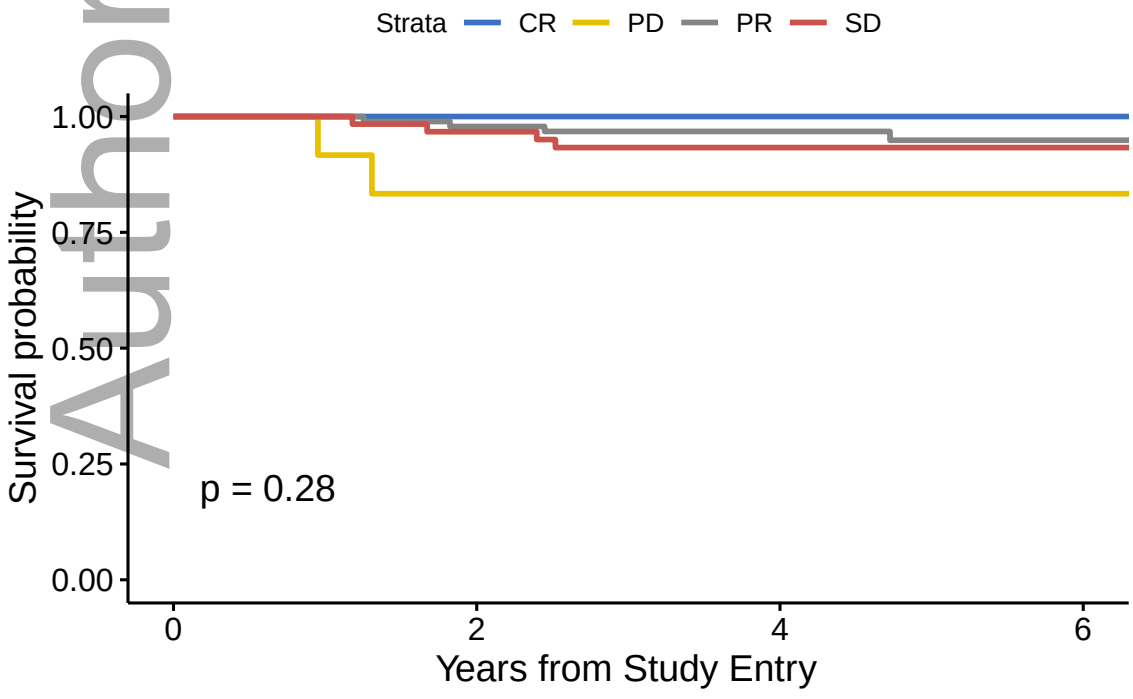


Number at risk

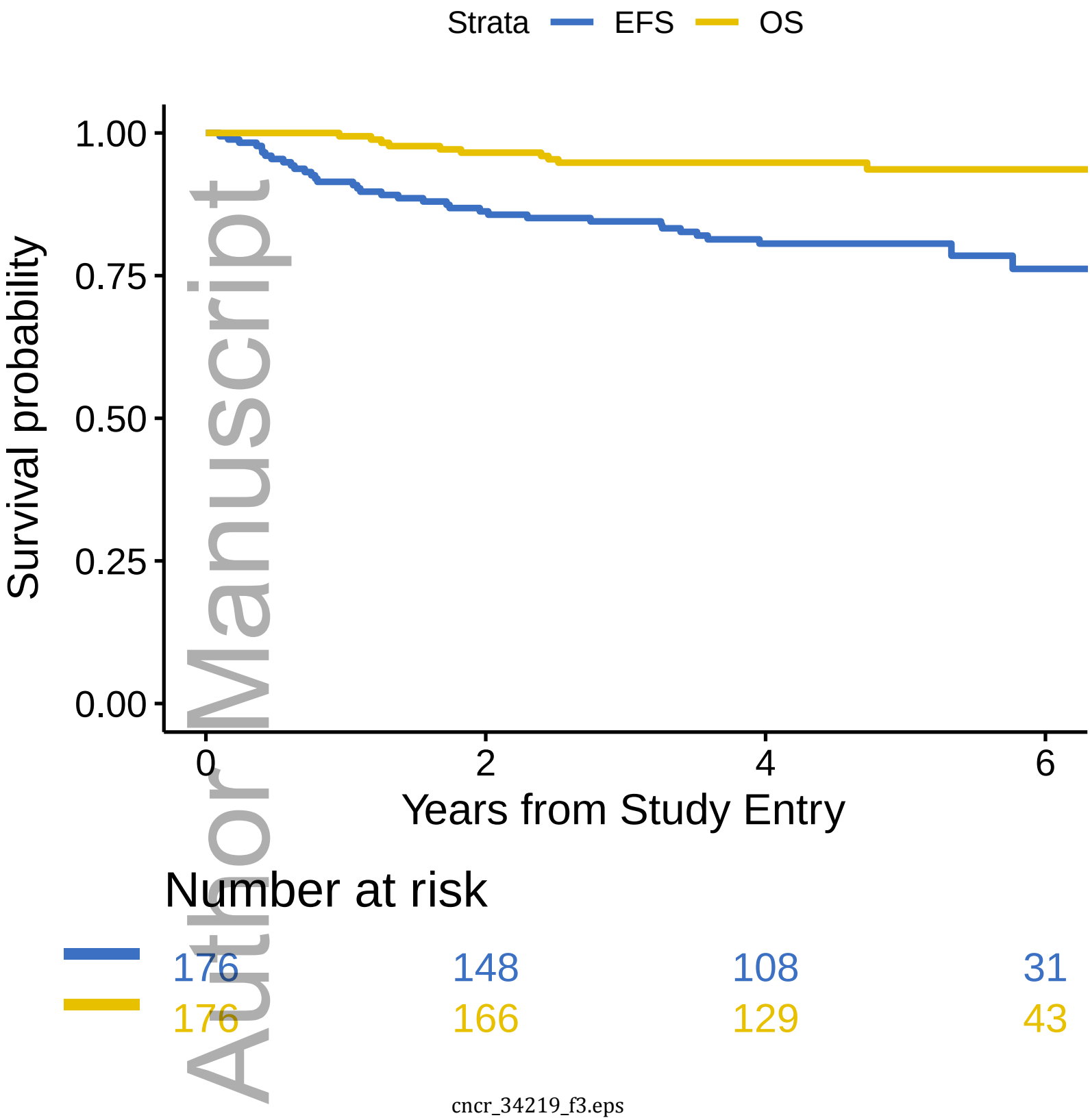
4	3	3	2	0
12	9	7	3	1
93	83	61	18	3
63	51	37	8	0

B



Number at risk

4	4	4	3
12	10	8	3



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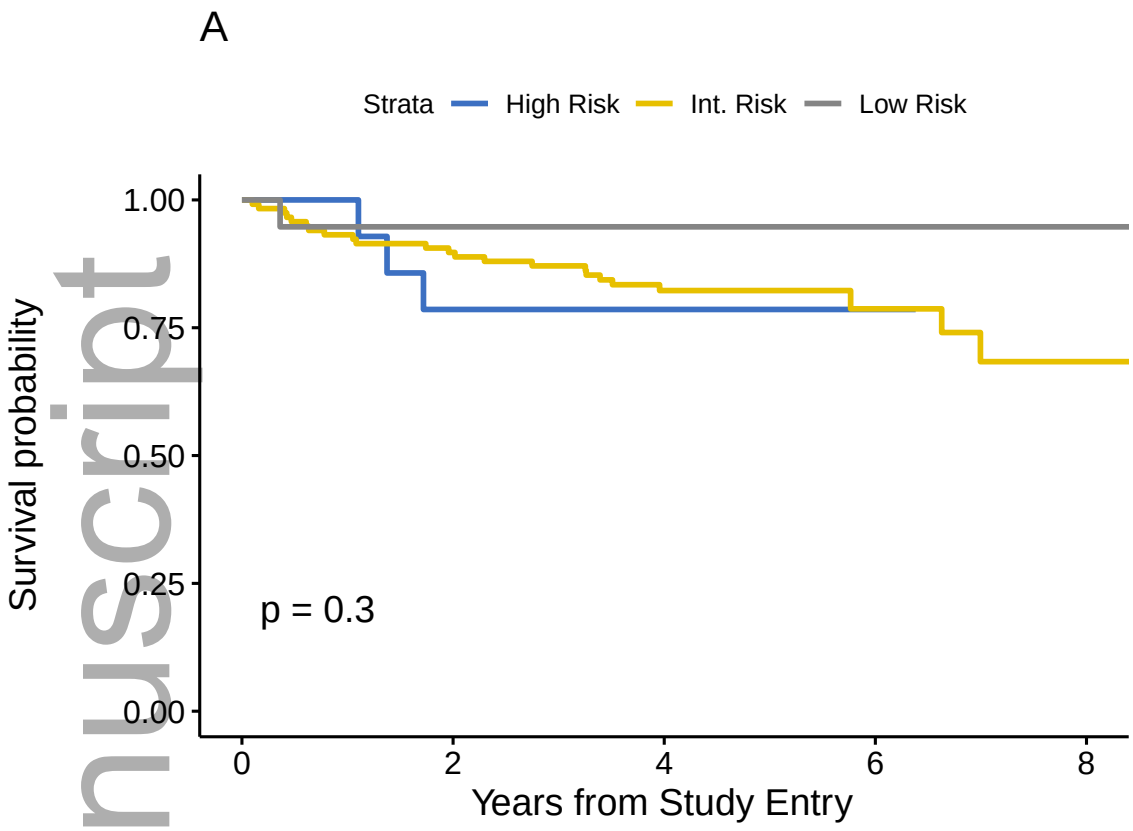
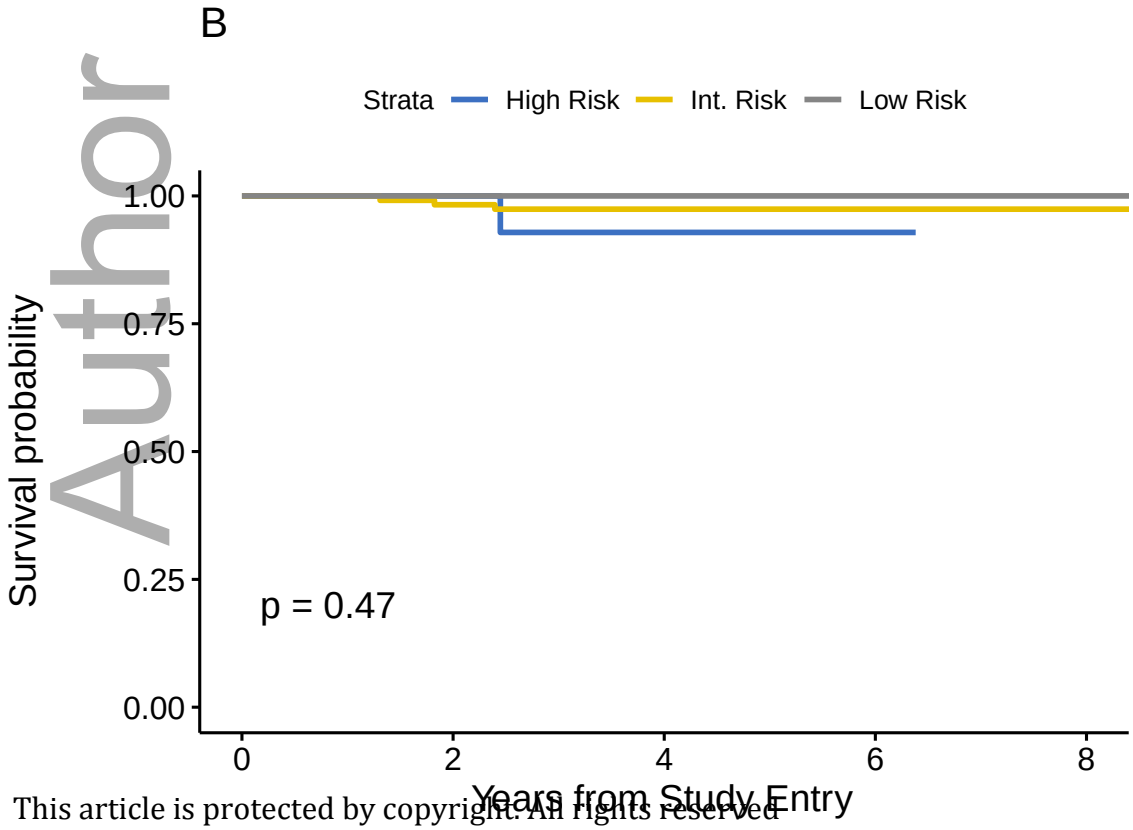


Number at risk

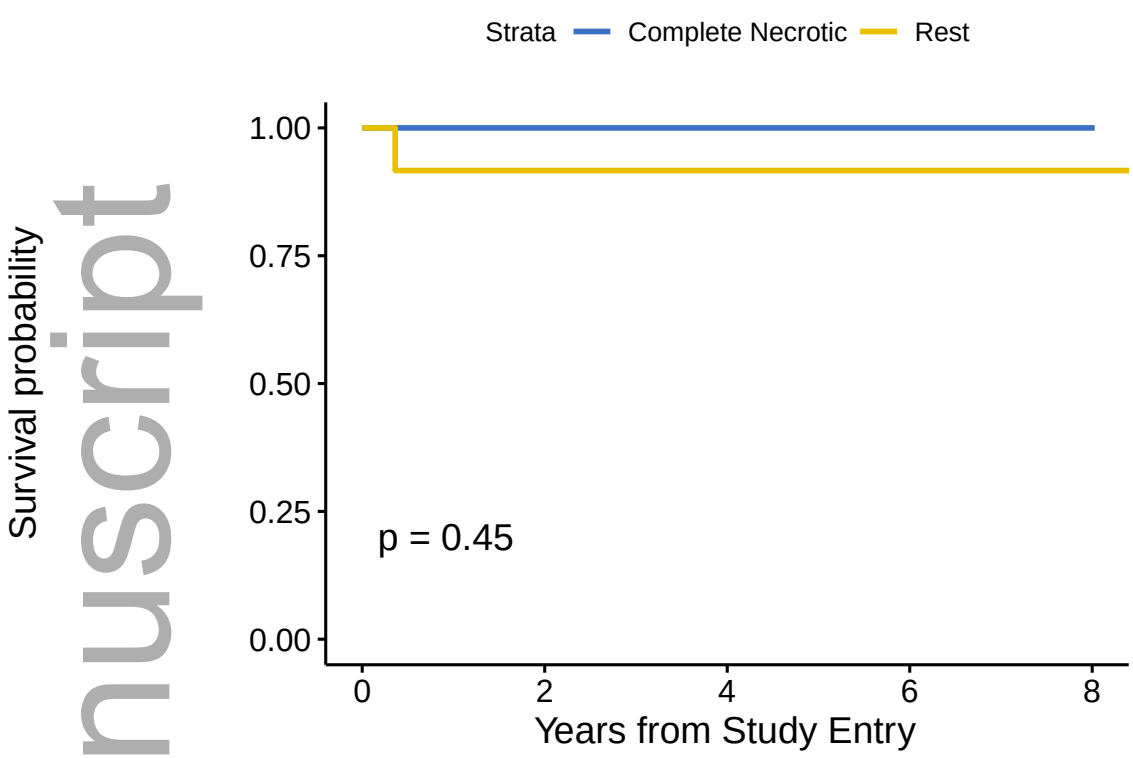
High Risk	14	11	10	3	0
Int. Risk	118	103	72	21	2
Low Risk	19	18	13	4	2



Number at risk

High Risk	14	14	12	2	0

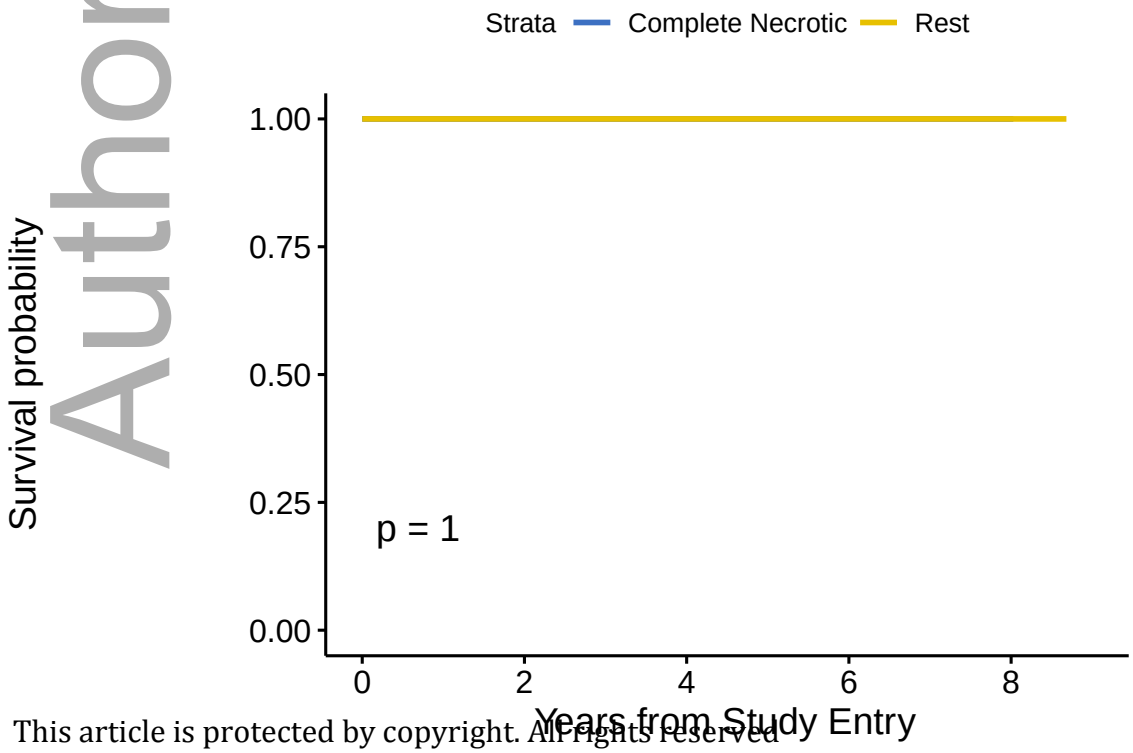
A



Number at risk

Complete Necrotic	7	7	4	2	1
Rest	12	11	9	2	1

B



Number at risk