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Local Control with Reduced Dose Radiotherapy for Low-Risk Rhabdomyosarcoma: A Report from the Children's Oncology Group D9602 Study

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Abstract

Purpose—To analyze the effect of reduced-dose radiotherapy on local control in children with low-risk rhabdomyosarcoma (RMS) treated on the COG D9602 study.

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Methods and Materials—Patients with low-risk RMS were non-randomly assigned to receive radiotherapy doses dependent upon the completeness of surgical resection of the primary tumor (Clinical Group) and presence of involved regional lymph nodes. After resection most patients with microscopic residual and uninvolved nodes received 36 Gy, those with involved nodes received 41.4 to 50.4 Gy, and those with orbital primaries received 45 Gy. All patients received vincristine and dactinomycin, with cyclophosphamide added for patient subsets that had a higher risk of relapse in IRSG III and IV studies.

Results—Three hundred forty-two patients were eligible for analysis; 172 received radiotherapy as part of their treatment. The cumulative incidence of local/regional failure was 15% in patients with microscopic involved margins when cyclophosphamide was not part of the treatment regimen and 0% when cyclophosphamide was included. The cumulative incidence of local/regional failure was 14% in patients with orbital tumors. Protocol-specified omission of radiotherapy in girls with Group IIA vaginal tumors (n=5) resulted in 3 failures for this group.

Conclusions—Compared to IRS III and IV results, reduced-dose radiotherapy does not compromise local control for patients with microscopic tumor after surgical resection or with orbital primary tumors when cyclophosphamide is added to the treatment program. Girls with unresected non-bladder GU tumors require radiotherapy for post-surgical residual tumor in order to achieve optimal local control.

Keywords

Rhabdomyosarcoma; Radiotherapy; Low-risk; Local Control

Introduction

The prospect of cure for children with rhabdomyosarcoma (RMS) has improved over the last three decades. Currently, children with favorable risk factors have a 5-year failure free survival (FFS) rate of greater than 85%¹. However, therapy for RMS is intensive, requiring multi-modality treatment with chemotherapy and surgery and/or radiotherapy (RT). Prior to this current study, the Intergroup Rhabdomyosarcoma Study Group (IRSG) studies focused primarily on exploring therapies to improve FFS. This recently completed generation of studies (D-series: D9602, D9802, and D9803) focused on risk-adapted therapy – investigating new treatment agents and strategies for those with average and high-risk disease, and minimizing therapy while maintaining good outcomes for those with low-risk disease. Previous IRSG protocols had typically used radiation doses of 41.4 Gy for patients with microscopic residual tumor after initial resection of the primary tumor, and 50.4 Gy or more for patients with gross residual tumor. The excellent results obtained in these trials in certain “low-risk” patient populations (defined below) presented the opportunity to investigate selectively decreasing the intensity of therapy for patients with favorable risk factors. Additionally, single-institution reports suggested that RT doses for microscopic residual RMS might be reduced without compromising local control^{2, 3}. In the Children’s Oncology Group (COG) low-risk study, D9602, a major objective was to decrease the dose of RT without compromising FFS when compared to results from the IRS III and IRS IV studies. This report details the results of this strategy on local control in children with low risk RMS.

Methods and Materials

Patients with RMS were categorized according to the IRSG pre-treatment staging system and the IRSG surgicopathologic group classification as detailed in Table 1⁴. Low-risk patients eligible for D9602 included all children with non-metastatic RMS in a “favorable” site (orbit, non-parameningeal head and neck, non-bladder/prostate genitourinary and biliary

tract) and children with non-metastatic RMS in an “unfavorable” site (bladder/prostate, extremity, parameningeal, or other not specifically listed as a favorable site) who had a gross total resection of all tumor (Group I or Group II) at the time of diagnosis (Figure 1). When first opened in September 1997, D9602 included previously untreated patients < 21 years old with a histologic diagnosis of embryonal RMS, ectomesenchymoma, alveolar RMS or undifferentiated sarcoma. After September 1999, eligibility criteria were changed to exclude patients with alveolar and undifferentiated histologies and move them to the “intermediate-risk” study D9803. The patients with embryonal RMS form the study population for this report. Clinical staging of regional lymph nodes was accepted for all patients initially, but beginning July 1999 regional lymph node sampling was required for all patients with extremity primary sites. Beginning March 2000, children 10 years of age with paratesticular primary tumors and normal staging CT of the abdomen and pelvis were required to have a staging ipsilateral retroperitoneal lymph node dissection prior to study entry⁵. Eligible patients were further stratified into two subgroups, A and B, based upon anticipated prognosis (Figure 1). Patients were required to start protocol therapy within 6 weeks of their initial surgical procedure.

Local Therapy

An initial surgical procedure was performed in all cases to obtain a histologic diagnosis. A more aggressive surgical procedure was performed if there was felt to be a chance of achieving a gross total resection without compromising function or cosmesis. Group I patients received no further local therapy. Group II and orbital Group III patients received RT beginning at week 3. Patients with nonorbital Group III tumors were re-evaluated for second look operation (SLO) at week 12. Children with Group III, lymph node-negative primary vaginal tumors responding to chemotherapy by week 12 were re-evaluated at weeks 20 and 28 for continued response. If biopsy and clinical examination at those times showed a complete response then no local therapy was given. If tumor persisted, SLO was considered. Post-operative RT was given only for post-operative residual gross or microscopic tumor. For other non-orbital Group III patients, SLO was performed at week 12 if gross total resection was considered possible without significant functional or cosmetic deficit, and RT was delivered following adequate healing from surgery. If SLO was not performed, RT began at week 12.

For children with Group IIA disease (microscopic residual viable tumor at the surgical margins), a dose of 36 Gy in 20 fractions was given to a volume described below. For Group IIB or IIC patients (involved lymph nodes without (B) or with (C) microscopic positive surgical margins), 41.4 Gy in 23 fractions was given. Children with Group III orbital tumors were treated with 45 Gy in 25 fractions. Children with nonorbital Group III primary tumors who did not undergo SLO received 50.4 Gy in 28 fractions (Table 2). Children who underwent SLO received RT according to the extent of the resection. Those with negative lymph nodes who had a gross total resection with or without microscopically negative margins received 36 Gy in 20 fractions (except for girls with vaginal tumors in whom no RT was given if they had had resection with negative margins). Patients with involved lymph nodes but no gross tumor were given 41.4 Gy in 23 fractions. Those with gross residual tumor received 50.4 Gy in 28 fractions.

RT target volumes were defined in accordance with ICRU 50 guidelines⁶. The Gross Tumor Volume (GTV) was defined as the pre-operative extent of tumor. For abdominal or thoracic primaries, if a tumor had originally displaced a significant amount of bowel or lung which subsequently returned to normal anatomic position following surgery and/or chemotherapy, then the GTV excluded the intra-abdominal or intra-thoracic portion of the tumor which had been “debulked”. However, all areas of preoperative involvement of the pleura, peritoneum and mesentery were retained within the GTV. The Clinical Target Volume (CTV) was

defined as the GTV plus 1.5 cm. If regional lymph nodes were involved, the CTV included the entire lymph node chain. The CTV did not extend outside the bony orbit for orbital primaries unless there was evidence of bony erosion. For patients with Group III tumor who did not undergo SLO, a cone-down boost was used after 36 Gy with the boost CTV defined as the GTV plus 0.5 cm. The Planning Target Volume (PTV) was defined as the CTV plus an institution-specific margin to account for day-to-day setup variation and physiologic motion of the CTV. For most patients, this margin was 0.5 cm.

All treatment was given using megavoltage radiation. Intensity Modulated Radiotherapy (IMRT) was allowed. Dactinomycin was withheld during RT.

Radiotherapy Quality Assurance

All RT fields and isodose distributions were reviewed by one of the study radiation oncologists. For patients planned with 2D technique, a minor protocol deviation was scored if 1) the dose to the prescription point differed from that in the protocol by more than 6% but less than 10%; 2) if the dose variation in the PTV exceeded +7% or -5%; 3) if the 95% isodose line covered <90% of the PTV or less than 100% but more than 90% of the CTV; or 4) if the margins for the CTV or PTV were less than specified or excessively large.

For patients planned with 3D technique, a minor deviation was scored if the dose to the prescription point differed from that in the protocol by more than 5% but less than 10%.

For either 2D or 3D techniques, a major deviation was scored if the delivered dose to the prescription point differed from the protocol by more than 10% or if the GTV did not include the entire pre-operative tumor volume.

Systemic Therapy

Chemotherapy doses were based on the age of the patient and changed during the course of the study, based on concerns relating to the incidence of hepatopathy⁷. Following initial surgery, most children received dactinomycin 0.045 mg/kg on day 1 of weeks 0, 3, 6, and 9 and vincristine 1.5 mg/m² (maximum 2.0 mg/dose) weekly for 9 weeks. Additionally, children in subgroup B received cyclophosphamide 2.2 g/m² with each dose of dactinomycin. This 12-week chemotherapy cycle was repeated a total of 4 times, resulting in a total of 48 weeks of systemic therapy. Details of chemotherapy administration will be reported separately⁸.

Statistical Analysis

FFS was defined as the time from the start of treatment to disease progression, recurrence or death as a first event. Overall survival (OS) was defined as the time from the start of treatment to death from any cause. The Kaplan-Meier method was used to estimate the FFS and OS distributions⁹. Recurrence was defined as local if tumor recurred at the site of primary disease, regional if the regional lymph nodes were involved, and distant if any metastatic disease was present at the time of recurrence. Only first recurrences were considered for this analysis. The cumulative rates of local/regional recurrence were estimated using cumulative incidence curves. Differences between curves were analyzed by the log-rank test¹⁰. Analyses were based on data available by February, 2008. The median follow-up was 5.1 years.

Results

Three hundred eighty eight patients were enrolled from September 1997 through September 2004. Forty six patients were ineligible, primarily because of ineligible histology or lack of

central pathology review, leaving 342 evaluable patients. Median patient age was 6.0 years (range 0 to 27 years). There were 219 (64%) male patients and 123 (36%) female patients. Breakdown by stage, Group and prognostic sub-group is given in Table 3. Regional lymph nodes were involved at diagnosis in only 17 patients (5%). RT was given as part of protocol treatment in 172 patients (50%). At last follow-up, 36 patients had experienced a local/regional failure at a median of 1.2 years (.05 – 6.0 years), and the 5- year cumulative incidence of local/regional failure was 11%. Ninety-two percent of all failures contained a component of local/regional failure.

Subgroup A Patients Treated with Reduced Radiotherapy Dose for Group IIA Tumors

62 patients had embryonal Group IIA disease treated without cyclophosphamide (Subgroup A) who, except for female patients with non-bladder genitourinary primaries, were to receive reduced-dose RT (36 Gy) (Table 4). Distribution by tumor site was orbit – 18, paratestis – 18, non-parameningeal head and neck – 14, non-bladder/prostate GU – 11, and biliary – 1.

The 5-year cumulative incidence of local/regional failure was 15% (8 local failures, 1 regional/distant failure). Three of these failures occurred in females with vaginal primary tumors (n=5) who, per protocol, did not receive RT. The other 6 failures occurred in paratestis (1 patient), vulva (1 patient), cervix (1 patient), and non-parameningeal head and neck (3 patients) sites. Of these 6, one had RT delivered per protocol, 3 had minor RT deviations, and 2 did not receive RT. Among the 53 patients without local/regional failure, there were 1 major and 11 minor RT deviations.

Subgroup B Patients with Embryonal Histology Treated with Reduced Radiotherapy Dose for Group II Tumors

Sixteen patients had embryonal Group IIA tumors in unfavorable sites (Subgroup B) and received 36 Gy and cyclophosphamide chemotherapy. No local failures have been observed (Table 5).

Subgroup A Patients Treated with Reduced Radiotherapy Dose for Group III Orbit Tumors

Seventy-seven patients had orbital embryonal Group III tumors that were treated with reduced-dose RT (45 Gy) without cyclophosphamide. Local failure occurred in 10 patients for a 5-year 14% cumulative incidence of local failure (Table 6). Of these, 5 had RT given per protocol. Two patients were taken off study prior to RT for progressive tumor, 1 patient had a major RT deviation, 1 had a minor deviation, and 1 was unevaluable for RT due to insufficient data.

Lymph Node-Positive Patients

Seventeen patients with embryonal histology had involved lymph nodes at the time of diagnosis and were assigned to receive 41.4 or 50.4 Gy for either microscopic or gross residual disease, respectively, after surgery. All of these patients also received cyclophosphamide. There were two failures in this group, both in patients with paratesticular tumors. One was a regional recurrence and the other a distant one. Both patients had appropriate RT per protocol.

Second Look Operation (SLO)

Twenty-one patients had Group III tumors in non-orbit and non-vagina sites and were eligible for SLO following 12 weeks of VAC chemotherapy. Seven (4 gall bladder/biliary tree, 2 head and neck, 1 vulva) of these patients underwent SLO. Three patients had a clinical complete response prior to SLO. At the time of exploration, one had microscopic

residual tumor on biopsy, one was free of tumor on biopsy, and one did not have a biopsy. All received reduced-dose radiotherapy of 36 Gy post-operatively. Two remain free of disease and one suffered a local relapse. Two patients had a clinical partial response prior to SLO; one had a sub-total resection of tumor and received 50.4 Gy post-operatively, and the other had a gross total resection and received 36 Gy post-operatively. Both remain free of tumor. Two additional patients with a clinical partial response received radiotherapy prior to SLO. The resected tumor showed microscopic residual tumor in one and no tumor in the other. Both patients remain free of recurrence. Of the 14 patients not undergoing SLO, 5 had local/regional failure.

Radiotherapy Compliance

Among the 172 patients with Group II/III disease who received RT, RT was judged “appropriate” per protocol in 92 (53%) of treated patients with 41 (24%) having minor deviations, 12 (7%) with major deviations and 27 (16%) unevaluable. The 5-year cumulative incidence of local/regional failure was 13% (11 of 92) among patients having no deviation and 6% (4 of 53) among patients with major or minor deviations. Four patients did not receive radiotherapy, though it was required by protocol guidelines. Age was a factor in 3 of these children, who were less than 2 years old at the time of diagnosis. Three children who did not receive radiotherapy had Group IIA disease and are alive without recurrence. The fourth child had a Group III orbit tumor and died of progressive disease.

Discussion

Local control continues to play a dominant role in the cure of patients with RMS – especially those with early-stage “low-risk” disease. Previous reports have found local/regional relapse to be the cause of the majority of failures^{11, 12} and in this current study, 92% of failures had a component of local relapse. However, there is increasing recognition of the adverse effects of surgery and radiotherapy on longterm survivors of childhood cancer¹³. Since overall local control and survival rates in patients with lowrisk RMS are high, a primary objective of this study was to determine whether the dose of RT could be reduced without compromising local control compared to IRS III and IRS IV outcomes.

Although withholding RT from patients with group II and III disease results in inferior local control^{14–16}, single-institution studies suggested that RT doses might be decreased from levels used in previous IRSG studies^{2, 3, 17}. Given the young age of this patient population, even modest reductions in RT dose could be beneficial in terms of long-term morbidity.

Patients with group IIA embryonal tumors in favorable sites had previously received 41.4 Gy on the IRS III and IV studies. Estimated 5-year cumulative incidence rates of local recurrence for this patient group on these studies were 11% and 2% respectively⁸. Using 36 Gy in the current study, the cumulative incidence of local failure was 15% (n=62) - a result that is comparable to that seen in IRS III. It is notable that 5 of the 8 failures in this group occurred in girls with non-bladder genitourinary tumors for an overall local control rate of only 50% for this disease site. Girls with vaginal tumors were treated with a local control paradigm that differed from all other tumor sites. Specifically, previous data had suggested that RT might not be required for girls with vaginal primaries if there was a complete response to chemotherapy and/or surgery^{18–20}. Therefore, none of the patients with vaginal tumors received RT as part of their treatment. Additionally, none of these patients received alkylating agents as part of their chemotherapy regimen. Cyclophosphamide and/or ifosfamide had been used for this patient group in IRS IV where local control was 98%, although not in IRS III where local control was 88%^{4, 21}. Considering the fact that 3 of the failures on the current study occurred in un-irradiated girls with vaginal primaries, and that alkylating agents were not part of the treatment regimen, there is no convincing evidence

that reduction of RT dose from 41.4 to 36 Gy was detrimental to tumor control. The efficacy of this dose reduction will continue to be studied in the current COG low risk RMS study, ARST0331. However, the high local failure rate in girls with vaginal primaries suggests that these tumors, in fact, are not a subset with any distinct biologic characteristics that might permit omitting RT for patients with post-operative residual tumor. A more detailed analysis of the inferior local control rate for vaginal RMS is reported in a separate manuscript²². In light of these results, COG ARST0331 has been amended to mandate RT for girls with Group II or III vaginal tumors (36, 41.4 or 50.4 Gy depending on extent of tumor).

The 5-year cumulative incidence of local failure for D9602 patients with embryonal histology Group III orbital tumors treated with 45 Gy without cyclophosphamide was 14%. This is greater than the 2% 5- year cumulative incidence rate for similar patients treated on IRS IV with 50.4 to 59.4 Gy and alkylating agent-containing chemotherapy. However, it is similar to the 16% cumulative incidence rate seen in Group III orbital tumors treated on IRS III using 41.4 Gy to 50.4 Gy (depending on patient age and tumor size) without an alkylating agent⁸. This suggests that reducing the RT dose to 45 Gy does not result in inferior local control for these children when cyclophosphamide is part of the regimen. In the current low-risk COG study, ARST0331, 45 Gy is being used for Group III orbital RMS tumors with the addition of cyclophosphamide to the chemotherapy regimen.

Patients with embryonal histology Group IIA tumors in unfavorable sites were treated with 36 Gy and cyclophosphamide-containing chemotherapy in this study, and no local failures were seen for 5-year cumulative incidence rate of local failure of 0%. This compares favorably to the 5-year cumulative incidence rates of local failure in similar patients of 16% in IRS III and 7% in IRS IV⁸. In both of these previous studies, the RT dose was 41.4 Gy with IRS IV also including an alkylating agent in the chemotherapy regimen. This result also suggests that the reduction in RT to 36 Gy did not result in an increased incidence of local failure.

One local recurrence was observed among the 17 patients with involved regional nodes. Previous analyses of patients with group III tumors found that regional lymph node involvement was the best predictor for local failure¹². The small number of node-positive patients in the current study does not allow statistical comparison, but the excellent local control rate does not suggest increased local failure risk for this group. Radiation dose for these patients in the current study was 41.4 Gy, similar to that used in previous protocols.

The use of SLO in this study was a new strategy for the IRSG, though it had been used by others^{2, 23}. Protocol guidelines allowed radiation dose reduction after SLO, but not the complete omission of RT. Other studies have supported the inclusion of radiation after SLO, even when all tumor is resected²³. Local control for this patient population was good, but the number of patients in this group was not large enough to allow for statistical comparison to other treatment paradigms.

Analysis of previous IRSG studies has suggested that outcomes are compromised when there are deviations from protocol-specified RT^{11, 24}. In D9602, only 7% of patients had major deviations from protocol-specified RT – a number too small to permit meaningful statistical comparison to patients treated in compliance with guidelines. It is pertinent to note that with time, the definition of compliance in terms of both dose and volume has evolved, so that today, patients who are treated “per protocol” in current studies might well have been scored as having minor or even major deviations according to previous criteria which generally required larger volumes and higher doses. It is quite possible that as treatment volumes and doses are decreased to the “true minimum”, compliance will become an even greater factor for outcome, emphasizing the need for expert treatment planning and delivery.

Although surgery and RT are the primary treatment modalities for achieving local control in RMS, there is evidence that chemotherapy also plays a role^{25, 26}. Our current study suggests that inclusion of an alkylating agent contributes to local control in this patient population. In all patient groups, local control rates were similar to those seen in IRS IV (which included cyclophosphamide or ifosfamide) if VAC was used, but were similar to the lower control rates seen in IRS III (no alkylating agent) if only VA was used. The inclusion of an alkylating agent carries the risk of increased long-term treatment morbidity, especially infertility and secondary malignancy. The current COG low risk RMS study, ARST0331, investigates a uniform but low cumulative dose of 4.8 mg/m² of cyclophosphamide with the hypothesis that modest exposure to cyclophosphamide will optimally balance the local control benefit of an alkylating agent against the risk of long-term morbidity. Optimal therapy for patients with low-risk rhabdomyosarcoma will require balancing local control and failure free survival with overall survival and toxicity.

Summary

In summary, this study supports the use of reduced RT doses for local control of RMS in lymph node-negative, low-risk patients with orbital primaries or microscopic tumor after resection. Cyclophosphamide-containing regimens are associated with lower rates of local failure for these patients. Non-bladder GU primary sites in girls do not appear to confer any special favorable biologic feature that would permit omission of RT, and therefore these children should receive RT/brachytherapy as part of their treatment regimen. The current COG RMS protocols continue the use of these reduced RT doses, with the addition of a moderate cumulative dose of cyclophosphamide.

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Figure 1.
Eligibility Criteria and stratification for the COG D9602 Low Risk Rhabdomyosarcoma Study

Table 1**Rhabdomyosarcoma Classification Systems**

Surgicopathologic Group Classification	
Group I: Localized disease, completely resected	
Group II: Gross total resection with positive margins and/or involved regional nodes	
IIA: Positive margins	
IIB: Involved regional nodes (resected)	
IIC: Both positive margins and involved, resected regional nodes	
Group III: Incomplete resection with gross residual disease	
Group IV: Distant metastatic disease at diagnosis	

TNM Staging System Definitions	
T1	Tumor confined to site of origin
a	≤ 5 cm
b	> 5 cm
T2	Tumor invading beyond site of origin
a	≤ 5 cm
b	> 5 cm
N0	No evidence of regional lymphatic spread
N1	Clinical or histologic involvement of regional nodes

Table 2

Radiotherapy Doses

Group	RT Dose (Gy)
I	No RT
IIA	36
IIB/C	41.4
III orbit	45
III non-orbit [#]	50.4

[#]These patients were eligible for SLO after week 12 chemotherapy. If completely resected, radiotherapy was reduced to 36 Gy for lymph-node negative tumors, and 41.4 Gy was given for lymph-node positive tumors. Girls with vaginal tumors received RT only if there was gross or microscopic tumor after chemotherapy +/- SLO.

Table 3

Characteristics of patients entered on D9602

	SubGroup A N=264, median follow-up = 5.2 years (0.0 – 9.9 years)	Subgroup B (embryonal histology only) n=78, median follow-up = 4.7 years (0.7 – 8.0 years)
Stage		
1	252 (97%)	55 (72%)
2	8 (3%)	9 (12%)
3	0	12 (16%)
Group		
I	122 (47%)	5 (6%)
IIA	62 (24%)	16 (21%)
IIB	0	12 (16%)
IIC	0	5 (6%)
III	77 (30%)	39 (51%)
Primary Site		
Paratestis	108 (41%)	17 (22%)
Uterus/cervix/vagina/vulva	19 (7%)	18 (24%)
Orbit	96 (37%)	2 (3%)
Head and Neck	29 (11%)	13 (17%)
Parameningeal	0	3 (4%)
Extremity	2 (1%)	4 (5%)
Other	7 (3%)	19 (25%)
Nodal Status		
N0	259 (99%)	58(76%)
N1	0	17 (22%)
Nx	1 (<1%)	1 (1%)

Table 4

Five-year Cumulative Local Control for Group IIA – Favorable Site Tumors N = 62, median follow-up = 4.8 years (0.2 – 9.1 years)

Protocol	Rate	RT Dose (Gy)	Chemotherapy	Local Failure
D9602 (n=62)	36		VA	15% *
IRS III (n=52)	41.4		VA	11%
IRS IV (n=43)	41.4		VAC/VAI/VAE	2%

I = ifosfamide, E = etoposide

* Five of 8 failures in D9602 occurred in girls with non-bladder genitourinary primaries who did not receive RT.

Table 5

Five-year Cumulative Local Control for Group IIA – Unfavorable Site Tumors N = 16, median follow-up = 4.8 years (0.7 – 7.9 years)

	RT Dose (Gy)	Chemotherapy	Local Failure Rate
D9602 (n=16)	36	VAC	0%
IRS III (n=38)	41.4	VA	14%
IRS IV (n=28)	41.4	VAC/VAI/VAE	7%

Table 6

Five-year Cumulative Local Control for Group III Orbital Tumors N = 77, median follow-up = 5.3 years (0.1 – 9.7 years)

	RT Dose (Gy)	Chemotherapy	Local Failure Rate
D9602 (n=77)	45	VA	14%
IRS III (n=71)	41.4–50.4	VA	16%
IRS IV (n=50)	50.4–59.5	VAC/VAI/VAE	4%