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SYSTEMATIC REVIEWS

Allograft tissue irradiation and failure rate after anterior cruciate ligament reconstruction: A systematic review

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Abstract

AIM: To evaluate whether anterior cruciate ligament (ACL) allograft irradiation is effective for sterility without compromising graft integrity and increasing failure rate.

METHODS: A literature search was conducted using PubMed, Cochrane, and Google. The following search terms were used: "Gamma irradiation AND anterior cruciate ligament AND allograft" with a return of 30 items. Filters used included: English language, years 1990-2015. There were 6 hits that were not reviewed, as there were only abstracts available. Another 5 hits were discarded, as they did not pertain to the topic of interest. There were 9 more articles that were excluded: Three studies were performed on animals and 6 studies were meta-analyses. Therefore, a total of 10 articles were applicable to review.

RESULTS: There is a delicate dosing crossover where gamma irradiation is both effective for sterility without catastrophically compromising the structural integrity of the graft. Of note, low dose irradiation is considered less than 2.0 Mrad, moderate dose is between 2.1-2.4 Mrad, and high dose is greater than or equal to 2.5 Mrad. Based upon the results of the literature search, the optimal threshold for sterilization was found to be sterilization at less than 2.2 Mrad of gamma irradiation with the important caveat of being performed at low temperatures. The graft selection process also must include thorough donor screening and testing as well as harvesting the tissue in a sterile fashion. Utilization of higher dose (\ge 2.5 Mrad) of irradiation causes greater allograft tissue laxity that results in greater graft failure rate clinically in patients after ACL reconstruction.

CONCLUSION: Allograft ACL graft gamma irradiated



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with less than 2.2 Mrad appears to be a reasonable alternative to autograft for patients above 25 years of age.

Key words: Anterior cruciate ligament reconstruction; Graft choice; Allograft; Gamma irradiation; Anterior cruciate ligament graft failure rate

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Core tip: The dose of gamma irradiation is directly correlated with increased failure rate of allograft in both *in vitro* and *in vivo* studies. Optimal gamma irradiation dose is less than 2.2 Mrad and should be performed in the setting of a low temperature.

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INTRODUCTION

Rupture of the anterior cruciate ligament (ACL) has been reported to have an incidence of 100000 to 200000 in the United States with about 400000 ACL reconstructions performed worldwide annually^[1,2]. ACL reconstruction is a common procedure in an orthopaedic sports medicine practice and has been shown to have favorable return to play outcomes and preservation of knee function. Both autograft (from the patient) and allograft (cadaver) can be used for the ACL reconstruction procedure^[3]. Advantages of autograft include lower graft failure rate in the young (< 25 years old) and active patient population, lower infection rate, and no risk of disease transmission or immune reaction^[4-7]. Alternatively, advantages of allograft include no donor site morbidity with decreased operative time, earlier return to sports and lower postoperative pain. In the older population, allograft has comparable outcomes compared to autograft reconstruction with a decrease in patient morbidity, surgical time, and smaller incision^[8]. Since using allograft tissue for ACL reconstruction (Figure 1) has proven to be successful in older patients with less physical demands, determining the most favorable processing method of the allograft tissue while minimizing catastrophic failure rates is of paramount importance.

For allograft tissue currently used, it must first undergo a detailed sequence of procedures that include medically and serologically screening donors to rule out viral contamination *via* nucleic acid testing. The Food and Drug Administration and the American Association of Tissue Banks have set industry standards for donor eligibility and tissue preparation. The donor is subjected to a rigorous physical and medical examination and an array of serological tests to detect antibodies for human immunodeficiency virus 1 and 2, hepatitis C virus, hepatitis B antigen, and syphilis^[9,10]. The rigorous donor selection process serves to eliminate specific contaminants by evaluating the allograft tissue's physical composition, including uniformity in shape and density as well as its biological properties to assess the level of microbial burden and risk for disease transmission^[9,11,12].

After appropriate graft donor selection has occurred, the next step is to sterilize the graft to a sterility assurance level (SAL) of 10⁻⁶ organism^[9,11,12]. There have been numerous preparations tested to determine the optimal sterilization method including peracetic acid and ethylene oxide, but many of the methods were abandoned after they were found to have detrimental effects on the mechanical properties of the graft and/or cause an inflammatory response in recipients^[13,14]. Other methods of sterilization, such as gamma irradiation, have proven to be more promising. This process uses a source emitting high-frequency electromagnetic radiation to disrupt the DNA (nucleic acids) of living organisms on the tissue to eliminate microbes and inactivating viruses^[15]. The International Atomic Energy Agency has developed a set of standards that govern the proper radiation sterilization of tissue allografts. Their protocol incorporates the principles that were put in place by the International Organization for Standardization to guide the radiation sterilization process of industrially produced health care products^[16].

Some authors cite that anywhere from 0.92-2.5 Mrads is needed to eliminate bacterial bioburden and fungal spores to achieve SAL of 10⁻⁶ on musculoskeletal allografts^[2,9,12,17,18]. However, the effect of gamma irradiation on viruses is controversial. It has been reported that, in order to inactivate human immunodeficiency virus (HIV) and hepatitis, doses as high as 4.0-5.0 Mrad are required^[17,18].

Unfortunately, gamma irradiation can have destructive effects on allografts by disrupting the polypeptide chain sequence and inducing minor crosslinking without interfering with collagen's normal banding pattern^[19]. There have been reports of gamma irradiation of 3 Mrad causing a reduction on the mechanical properties of the allograft tissue^[20]. Additionally, the temperature at which the gamma irradiation is performed is also important to consider. The mechanical destruction has been reported to be lessened when grafts were irradiated at low temperatures (i.e., on dry ice) when compared to the same process performed at room temperature^[17,21]. However the production of free radicals has also been cited to be a benefit of performing irradiation at higher temperature as the free radicals have anti-microbial effects^[17].

The balance between sterilization of the allograft tissue without compromising the biomechanical properties, strength and functional outcomes is a topic of debate. The purpose of this systematic review article is to further explore the effect of gamma irradiation on Dashe J et al. Allograft tissue irradiation and failure rate after ACL



Figure 1 Non-irradiated Achilles allograft tissue. A non-irradiated Achilles tendon allograft used in an anterior cruciate ligament reconstruction procedure.

the catastrophic failure rate and functional outcomes in patients after ACL reconstruction with allograft tissue.

MATERIALS AND METHODS

Systematic review of clinical studies

A literature search was performed using PubMed, Cochrane, and Google with the following search terms with a return of 30 items: "Gamma irradiation AND anterior cruciate ligament AND allograft". Filters used included: English language, years 1990-2015. There were 6 items that were not reviewed, as there were only abstracts available. Another 5 articles were discarded, as they did not pertain to the topic of interest. There were 9 more articles that were excluded: Three studies were performed on animals and 6 studies were metaanalyses. Therefore, a total of 10 clinical articles were applicable to review (Figure 2).

RESULTS

With regards to the effects from gamma irradiation, there are several articles that have extensively studied the effects of irradiation on ACL grafts (Tables 1 and 2). There were four prospective, randomized trials by the same author who attempted to answer this question. The results of these studies all demonstrated that patients who had allografts exposed to > 2.5 Mrad of irradiation had a significantly greater laxity than autograft or nonirradiated allografts; however there were no significant differences in any of these studies on the International Knee Documentation Committee (IKDC) outcome scores or range of motion^[22-25]. Unfortunately, none of these studies report graft temperature during irradiation and therefore should be interpreted with caution. As stated earlier, it is important that the grafts be irradiated at low temperatures to decrease the free radical formation as to not weaken the allograft biomechanical properties^[17,21].

Rappé *et al*^[18] conducted a cohort study comparing non-irradiated Achilles allografts to irradiated Achilles allografts (2.5 Mrad) with the primary outcome of clinical failure (positive Lachman exam, magnetic resonance imaging, and/or side-to-side difference of 5 mm or

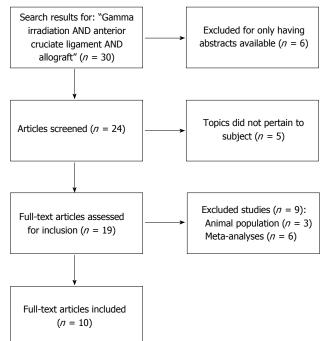


Figure 2 Systematic review of the literature with exclusion and inclusion criteria.

greater on KT-1000 exam). They found that there was a significant difference in clinical failures between the irradiated (33.3%) and non-irradiated groups (2.4%; P < 0.01)^[18]. However, there are weaknesses to their study, including a large loss of follow-up in the irradiated group (27%) compared to the non-irradiated group (7%); additionally there was no mention of the temperature at which the irradiation process was performed.

Rihn *et al*^[26] compared the outcomes of bonepatella-tendon-bone (BTB) autograft to BTB allograft that underwent 2.5 Mrad of irradiation. They found no differences in the rate of return to sports or the IKDC scores; however, objectively, the allograft group had significantly more laxity on KT-1000, Lachman exam, and pivot shift clunk. However, similar to Rappé *et al*^[18], this study made no mention of temperature of the graft preparation and had significant differences in the mean age of the two study groups with the allograft group having an older mean age.

The increase in laxity and failure rates was also noted in the studies by Sun *et al*^[22-25] with 34% failure seen in the irradiated allograft group (2.5 Mrad), 6.4% in the autograft group and 8.8% in the nonirradiated allograft group. Sun *et al*^[23] compared hamstring autograft to irradiated allograft with over 2.5 years of follow-up and reported the rate of laxity was 32% higher in the irradiated *vs* autograft group (8.3%). In addition, anterior and rotational stability also decreased significantly in the irradiated allograft group; however, the IKDC functional scores were very similar between the two groups. In a subsequent follow-up randomized controlled trial comparing irradiated to nonirradiated hamstring allograft for ACL reconstruction, Sun *et al*^[24] found that allograft irradiation is responsible for increased anterior and



Table 1 In	<i>vivo</i> stud	lies of non-irra	Table 1 $$ In vivo studies of non-irradiated and irradiated allograft tissue for	ated allogra	ft tissue for anterior ci	ruciate I	igament	anterior cruciate ligament reconstruction			
Ref.	Year	Type of study	Graft type	Irradiation dose	No. of patients (at final follow-up/enrolled)	Male F	emale /	Female Average age (yr)	Follow-up length	Findings	Weaknesses
Rihn <i>et a</i> l ^[26]	2006	Retrospective	Retrospective BPTB - allograft	2.5 Mrad	39	27	12	44 ± 8.4	4.2 yr	Significant difference between irradiated allograft and allograft with laxity, Lachman, and pivot shift clunk	Age difference in populations
			BPTB - autograft	None	63	43	20	25.3 ± 9.3	4.6 yr	No significant difference on range of motion, effusion, IKDC, KT-1000 when adjusted for age, IKDC physical event reling and rehim to short	No mention of temperature when irradiation nerformed
Rappé <i>et al</i> ^[18]	2007	Cohort	Achilles - allograft	2.0-2.5 Mrad	33/45	N/A	N/A 2	26 (ranage 14-59)	6 mo		Large loss of follow- up in irradiated group
			Achilles - allograft	None	42/45			27 (range 14-57)			No mention of temperature when irradiation performed
Sun et al ^[22]	2009	Prospective, randomized	BPTB - allograft	2.5 Mrad	32/33	24	œ	30.1 ± 6.1	31 mo (2% lost to follow-up)	≡ s _ n	No mention of temperature when irradiation performed
			BPTB - autograft	None	33/33	24	0	29.7 ± 7.2		No significant difference on overall IKDC, range of motion, Harner's vertical jump test, Daniel's one-leg hip test, subjective IKDC, Cincinnati knee score, Lysholm score, and Tener score	
$\operatorname{Sun} et al^{[23]}$	2009	Prospective, randomized	BPTB - allograft	2.5 Mrad	32	24	×	30.1 ± 6.1	31 mo (1% lost to follow-up -	Significant difference between irradiated allograft, non-irradiated allograft, snd autograft	No mention of temperature when
			BPTB - allografi	None	34	22	12	31.8±6.9 ti	treatment group not mentioned)	with greater laxity on KT-2000, side to side difference on KT-2000, pivot shift grade II or III, anterior drawer test grade II or III, and Lachman test grade II or III	irradiation performed
			BPTB - autograft	None	33	24	6	29.7±7.2		No significant difference on overall IKDC, range of motion, Harner's vertical jump test, Daniel's one-leg hip test, subjective IKDC, Cincinnati knee score, Lysholm score, and Tener score	
Sun et al ^[24]	2011	Prospective, randomized	Hamstring - allograft	2.5 Mrad	31/37	24	~	30.3±7.9 4	42.2 mo (11% lost to follow-up)	Significant difference between irradiated allograft and autograft with greater laxity on KT-2000, side to side difference on KT-2000, pivot shift grade II or III, anterior drawer test grade II or III, and Lachman test grade II or III	No mention of temperature when irradiation performed
			Hamstring - autograft	None	36/38	28	×	30.9 ± 8.7		No significant difference on overall IKDC, range of motion, Harner's vertical jump test, Daniel's one-leg hip test, subjective IKDC, Cincinnati knee score, Lysholm score, and Tegner score	

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Significant difference between irradiated No mention of allograft and non-irradiated allograft with temperature when greater laxity on KT-2000, side to side difference irradiation performed on KT-2000, pivot shift grade II or III, anterior drawer test grade II or III, and Lachman test grade II or III	ce on overall IKDC, r's vertical jump test, st, subjective IKDC, Lysholm score, and score
	No significant difference on overall IKDC, range of motion, Harner's vertical jump test, Daniel's one-leg hip test, subjective IKDC, Cincinnati knee score, Lysholm score, and Tegner score
42.5 mo (9.1% lost to follow-up)	
30.3 ± 7.9	31.7 ± 7.8
▶	▶
24	31
31/38	38/39
2.5 Mrad	None
Prospective, Hamstring- randomized allograft	Hamstring - allograft
Prospective, randomized	Hamstring - None 38// allograft
2012	
Sun <i>et al</i> ⁽²³⁾	

IKDC: International Knee Documentation Committee; BPTB: Bone patella tendon bone.

otational instability. Furthermore, the knees that had an ACL reconstruction done with the irradiated graft has significantly more osteoarthritis compared to the nonirradiated group

ound no significant difference between the irradiated group and the non-irradiated groups when testing the grafts' tensile strength. Balsly et al^{ig} also reported on the effect of All irradiation processing was performed at low temperatures. For the low dose irradiation groups for all types of allografts mentioned, there were no significant difference found In biomechanical testing, Roche *et al^[27]* evaluated the effect on gamma irradiation (1.55 Mrad on dry ice or low temperature) with BTB and fascia lata allografts. The authors between the control groups and the low dose irradiation groups when the tensile strength or modulus of elasticity of the grafts was tested. For the moderate irradiation group, low (1.8-2.2 Mrad) vs high dose (2.4-2.8 Mrad) irradiation on the biomechanical properties of allograft tissue (BTB, anterior tibialis, semitendinosus, and fascia lata allografts). there was either a significant difference or a trend towards having a significant difference when compared to the controls in these same measures.

Fideler et al²⁸¹ also demonstrated that the initial biomechanical strength of allografts was reduced 15% when compared to controls after 2 Mrad of irradiation. He also \$ ailure of irradiated patellar tendon grafts vs nonirradiated grafts was 1965 ± 512 N vs 2457 ± 647 N, respectively. Furthermore, with cyclic loading, the irradiated grafts showed a dose dependent effect on the integrity of the allograft tissue with increasing gamma irradiation at 3 and 4 Mrads. Curran et alization the average load elongated 27% more than the nonirradiated grafts (P < 0.05)

DISCUSSION

The choice of graft for ACL reconstruction is contingent upon many factors including the age, baseline level of activity, and planned level of future activities^[2,3,30]. Much of the debate about whether to use allograft or autograft for ACL reconstruction is related to the morbidity and complications related to each option. Autograft procedures have the isks include quadriceps or hamstring weakness from quadriceps/hamstring grafts and anterior knee pain from the BTB procedures. The benefits of using autograft include disadvantage of increased surgical time due to graft harvesting, which can translate into higher procedural costs (i.e., operating room time). Additional autograft harvesting minimal risk of infection/disease transmission from donated tissue, no possibility of immune reaction to the graft, no cost of the graft (other than increased OR time), and an overall decreased rerupture rate in younger patients under the age of 25 years^[2,3,11,22,31]

nclude smaller incisions, reduced postoperative pain/less donor site morbidity (since no graft harvesting is required), larger graft availability, earlier postoperative knee range of axity over time, which can result in knee laxity and failure to return to previous level of activities despite an "intact" graft¹³¹. Some of the cited advantages of using allograft it has been reported that HIV or hepatitis transmission is 1 in 1.6 million^[29,17,18,21,26,31,32]. The possibility of an immune reaction stems from the body's response to foreign tissues via nteractions to human leukocyte antigens (HLAs) on donor cells. Fortunately, recent studies have found that an immune response to allograft tissue has not been a common ssue, since the allograft tissue processing (*i.e.*, the freezing process) essentially eliminates active HLA markers^[2,31]. Another cited disadvantage of allograft use is increased Reconstruction using allograft has its own unique risks. There are risks of immunogenic reaction, bacterial infection, and disease transmission from the graft donor. However,

Ref.	Year	Type of study	Graft type	Irradiation dose	Temperautre when irradiated	No. of samples	Age (yr)	Findings
Balsly et al ^[9]	2008	Laboratory	BPTB - low dose	1.83-2.18 Mrad	- 20 °C to -50 °C	9	18-55	There was a significant difference for:
			BPTB - moderate dose	2.4-2.85 Mrad		9		(1) BPTB - tensile strength in the moderate dose irradiation
			BPTB - control	None	N/A	9 controls for low dose 9 controls		<i>vs</i> control groups (2) Fascia lata - modulus of elasticity in the moderate
						moderate dose		dose irradiation <i>vs</i> control groups
			Anterior Tibialis - low dose Anterior Tibialis -	1.83-2.18 Mrad 2.4-2.85	- 20 ℃ to -50 ℃	10 10	23-64	No significant difference between the tensile strength and modulus of elasticity for
			moderate dose Anterior Tibialis - control	Mrad None	N/A	10 controls for		all other groups for low dose irradiation vs control and
			Anterior Tiblais - control	none	IN/ A	low dose 10 controls for moderate dose		moderate dose irradiation vs control (other than stated
			Semitendinosus - low dose	1.83-2.18 Mrad	- 20 °C to -50 °C	8	al 16-54	above)
			Semitendinosus - moderate dose	2.4-2.85 Mrad		10		
			Semitendinosus - control	None	N/A	10 controls for low dose 10 controls for		
			Fascia Lata - low dose	1.83-2.18	- 20 °C to -50 °C	moderate dose 10	19-48	
			Fascia Lata - moderate	Mrad 2.4-2.85		10		
			dose Fascia Lata - control	Mrad None	N/A	10 controls for low dose 10 controls for moderate dose		
Greaves <i>et al</i> ^[17]	2008	Laboratory	Tibialis - single strand irradiated (age < 45)	1.46-1.8 Mrad	Dry ice temperatures	10 irradiated	< 45	No significant difference in failure loads for irradiated v
			Tibialis - single strand non-irradiated (age < 45) Tibialis - double strand			10 non- irradiated 10 irradiated		non-irradiated for each of th three age groups (midsubstance failure =
			irradiated (age < 45) Tibialis - double strand			10 non-		any rupture within graft substance, grip failure =
			non-irradiated (age < 45) Tibialis - single strand irradiated (age 46-55)			irradiated 13 irradiated	46-55	slip from 1 of tendon grips exposing serrated portion of tendon)
			Tibialis - single strand non-irradiated (age 46-55) Tibialis - double strand			13 non- irradiated 10 irradiated		
			irradiated (age 46-55) Tibialis - double strand non-irradiated (age 46-55)			10 non- irradiated		
			Tibialis - single strand irradiated (age 56-65)			10 irradiated	56-65	
			Tibialis - single strand non-irradiated (age 56-65) Tibialis - double strand irradiated (age 56-65)			10 non- irradiated 10 irradiated		
			irradiated (age 56-65) Tibialis - double strand non-irradiated (age 56-65)			10 non- irradiated		
Baldini <i>et al</i> ^[34]	[34] 2012	12 Laboratory	Tibialis	2.0-2.8 Mrad	Not reported	15	41.8	There were no significant difference in stiffness, failur
					None		12	47.4



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Yanke <i>et al</i> ^[35]	2013	Laboratory	BPTB	1.0-1.2	Not reported	10	52 ± 11	There was a significant
				Mrad				difference in stiffness
				None		10		between the irradiated vs
								non-irradiated groups but
								none found in strain and
								elongation

BPTB: Bone patella tendon bone.

motion, and decreased surgical time^[2,11].

A discussion with patients about graft integrity is important when allograft is being used for ACL reconstruction. There have been reports about having decreased allograft strength after gamma irradiation, which clinically manifests as laxity and/or catastrophic graft failure. This has been a controversial topic with conflicting studies attributed to the lack of details about how grafts were processed including the irradiation dose and the graft temperature during irradiation^[9,17,18,21,26,32]. Our review of the literature found that utilizing the higher dose (≥ 2.5 Mrad) of irradiation causes greater allograft tissue laxity and subsequently increased graft failure rate. However, in the subset of patients that did not have catastrophic failures from the irradiated graft, overall functional outcome as measured by the IKDC scores were similar to the nonirradiated allograft or autograft groups. Ghodadra et al^[33], compared BTB autograft and Patellar tendon allograft (nonirradiated and low dose irradiation -1.0 to 1.3 Mrad) using a retrospective cohort and found no differences in postoperative laxity (KT-1000) or failure rates at 6 wk and 1 year. Additionally, the authors found no difference in the laxity between the patellar tendon groups that had the low dose irradiation vs no irradiation.

The choice to use an irradiated graft is contingent upon many factors. The important details to know when choosing an irradiated graft are: How the graft was prepared, the dose range of irradiation used, and the temperature of the graft when the irradiation was performed. The results from our systematic review suggest that grafts that are irradiated at low temperatures with 1.8 to 2.2 Mrad of irradiation do not appear to have deleterious effects on the allograft tissue tensile strength or elasticity modulus. However, moderate to high doses of gamma radiation (\geq 2.5 Mrad) will have a major impact on the allograft tissue biomechanical properties which may result in increased laxity that may compromise clinical outcomes and increase rates of functional failure. These above studies suggest that grafts irradiated at low temperatures with less than 2.2 Mrad of irradiation are an acceptable choice to optimize the benefits of sterility and without affecting rate of functional or catastrophic structural failure.

There have been large advancements in allograft tissue processing for ACL reconstruction over the past several decades. There are many advantages of using allograft for ACL reconstruction in the older and less active population when compared to autograft with similar functional outcomes. The concerns of infection with allografts have been mitigated by the changes in the tissue bank facility practices with improved donor tissue screening and use of gamma irradiation. Irradiation has proven to be successful at reducing the bioburden found on allografts (and possibly viral contamination) and appears to not have an effect on the rate of functional failure if it is performed with low dose irradiation (< 2.2 Mrad) at low temperatures. Grafts prepared with higher dose irradiation (\geq 2.5 Mrad) may be weakened and the additional irradiation may compromise the graft's biomechanical properties and clinical outcomes resulting in unacceptable failure rates.

COMMENTS

Background

Anterior cruciate ligament (ACL) reconstruction is a common procedure in the orthopaedic sports medicine practice. The surgery involves using tissue either from the patient (autograft) and/or from cadaver (allograft). It has been shown that the failure rates when comparing allograft to autograft tissue decreases with increased age.

Research frontiers

One of the main concerns with the use of allograft is the balance between the process of graft sterilization and its potential impact on graft integrity. It has been suggested that there is an association between increased gamma irradiation dosage and an adverse impact on the biomechanical properties of the allograft tissue, although controversy remains with regards to dosing thresholds that will compromise the strength of the allograft tissue.

Innovations and breakthroughs

There has been a trend toward increased allograft use in older and lower demand patients in recent years in an effort to decrease the morbidity associated with autograft harvest. With increased allograft use, appropriate graft irradiation exposure has been investigated. Four prospective, randomized trials demonstrated that patients who had allografts exposed to greater than or equal to 2.5 Mrad of irradiation had a significantly greater laxity and clinical failure rates than autograft or non-irradiated (< 2.2 Mrad) allografts (all different studies), but temperature at time of irradiation was not recorded. It is also important that the grafts be irradiated at low temperatures to decrease the free radical formation as to not weaken the allograft.

Applications

The authors used a systematic review of the currently available literature to determine that there is a delicate dosing crossover where gamma irradiation is both effective for sterility without catastrophically compromising the graft structural integrity.

Terminology

Gamma irradiation is a means of allograft sterilization, which uses a source emitting high-frequency electromagnetic radiation to disrupt the DNA (nucleic acids) of living organisms on the tissue.

Peer-review

This is a useful systematic review on the use of allograft for ACL reconstruction particularly focusing on the effect of the sterilization process on its biomechanical properties and clinical outcomes. The authors introduce the reader to the ACL reconstruction graft options, sterilization process and associated clinical and laboratory results. This review gives readers the opportunity to implement to their



practice a better use and understanding of gamma irradiation of allograft tissues for ACL reconstruction.

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